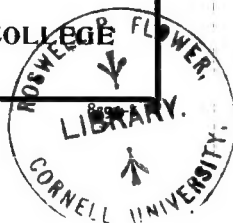
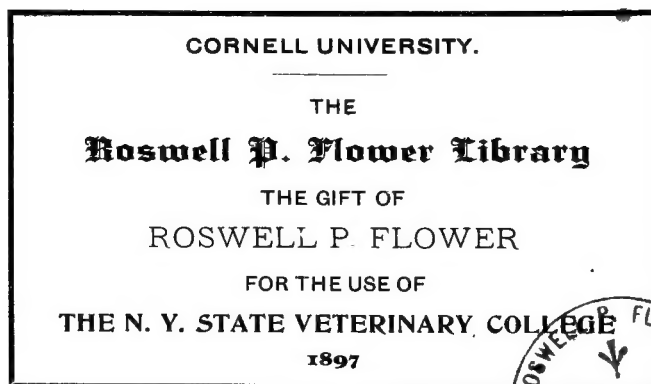


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APPENDIX
TO THE
REFERENCE HANDBOOK
OF THE
MEDICAL SCIENCES

BY VARIOUS WRITERS

REVISED TO DATE

EDITED BY
THOMAS L. STEDMAN, A.M., M.D.

NEW YORK
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THIS VOLUME IS A CONTINUATION OF VOLUME VIII FROM PAGE 342 OF THAT VOLUME.

IN THE GENERAL INDEX IN THIS VOLUME, REFERENCES TO VOLUME VIII, PAGES 343 TO 732, REFER TO THIS VOLUME.

APPENDIX.

Acidosis and Acid Intoxication.

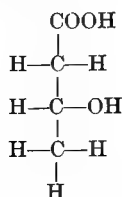
ACIDOSIS AND ACID INTOXICATION.—*Definition.*—While in a large part of medical literature acidosis and acid intoxication are used as synonymous terms, strictly speaking they represent quite distinct entities.

Acidosis may be defined as a condition, pathological or otherwise, in which an excess of acid products is indicated by an analysis of the blood or of the urine. It is impossible in many cases to distinguish whether an excess of acid products has really been formed, or whether the normal amount only has been formed and this amount has been inhibited from undergoing further oxidation. In conditions such as diabetes it is quite certain that the amount of acid products eliminated is in excess of what may be formed during normal metabolism. In this condition, at least, one is forced to assume that an excessive *production* of acid compounds takes place.

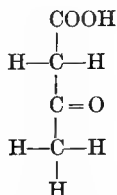
Acid intoxication, on the other hand, distinctly implies a pathological condition of toxic character produced by acid products formed within the organism. Acid intoxication may also be produced by the administration of acids, chiefly inorganic. This form of poisoning is of importance, as it has a comparative bearing on the general problem of acid intoxication.

The Compounds Taking Part in Acidosis.—The compounds immediately concerned in the problem of acidosis are three: β oxybutyric acid, acetoacetic acid (diacetic acid), and acetone. They are usually termed the acetone compounds, although it would be more advisable to speak of them as the oxybutyric acid compounds, for this substance is the starting-point in the formation of the other two.

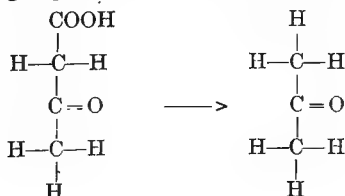
β oxybutyric acid has the formula:



This by oxidation is converted into acetoacetic acid:



which by losing a molecule of carbon dioxide from the carboxyl group is converted into acetone:



β oxybutyric acid was discovered simultaneously by Minkowski and by Külz, although Stadelmann had previously been led to suspect the presence of an abnormally large amount of an organic acid in diabetic urines. He mistook a decomposition product of β oxybutyric acid, α crotonic acid, for the former. β oxybutyric acid as formed in the body is a levorotatory syrup, which has been obtained by Magnus-Levy in a crystalline condition. Ferric chloride does not give a red color with this acid.

The presence of acetoacetic acid in the urine was indicated by the reaction discovered by Gerhardt, who found that certain urines gave a Bordeaux-red color when treated with an aqueous solution of ferric chlorid. Further investigation of this color reaction, especially by v. Jaksch, led this observer to believe that he had isolated acetoacetic acid from the urine. From the unstable character of this acid it is safe to say that it has never been separated from the urine in a pure condition. There is no doubt, however, that the substance giving the red color is really acetoacetic acid. All the tests which urines give under these conditions are those of aqueous solutions of acetoacetic acid. The acid is extremely unstable, and rapidly breaks down in solution into carbon dioxide and acetone.

Acetone was discovered in the urine by Petters and by Kaulich in 1857, and was the first of the acetone compounds to be detected. It is therefore from an historical point of view that acetone has lent its name to this class of compounds.

When attention was first drawn to the connection between β oxybutyric acid, acetoacetic acid, and acetone, it was thought that acetone was the first substance to be formed. This by synthesis with, possibly, formic acid would yield acetoacetic acid, which on reduction might be transformed into β oxybutyric acid. This has since been shown not to be the case. The administration of acetone has never been followed by an increase in the amount of either acetoacetic acid or β oxybutyric acid, while the converse almost invariably happens. The administration of β oxybutyric acid or acetoacetic acid to diabetics or to persons abstaining from food is followed by an increase in the acetone content of the urine and of the breath.

Furthermore, these compounds make their appearance in the urine in the following order: acetone, acetoacetic acid, β oxybutyric acid. They disappear in the reverse order, β oxybutyric acid being the first to vanish. As β oxybutyric acid is the last to appear and the first to leave, one can only conclude that its appearance indicates the greatest departure from normal metabolism, and that, being the first product formed, it only appears in the urine when the capacity of the organism to convert it to acetoacetic acid and acetone is impaired.

One other acid product of metabolism may be mentioned which has played no inconsiderable rôle in some late theories of acid intoxication. This is sarcocollac acid. It may be connected with the acetone compounds, but the relation, biologically, is not clear. Its place in acid intoxication will be discussed when eclampsia is considered.

The Source of the Acetone Compounds.—Theoretically all three classes of compounds which enter into tissue formation—carbohydrates, fats, and proteins—may be the sources from which the acetone compounds are derived.

As, however, the carbohydrates occupy such an exceptional place in the mechanism of acetone-compound formation, the latter two classes, viz., proteins and fats, can only be considered as being acetone formers.

For a long time it was thought that the fats and fatty acids alone were the source of the acetone compounds, but later work has served to assign to them a more or less secondary place, and to make the proteins, or, what is the equivalent, the amino acids, the chief source of these compounds.

According as a substance produces or inhibits the formation of acetone, it is classed as *ketogenic* or *keto-plastic*, or *antiketogenic* or *antiketoplastic*. Borchardt further subdivides the ketogenic compounds into those from which acetone is directly derived, which actually break down, yielding acetone or one of its forerunners, and those which are merely ketoplastic, that is to say, only increase the output of these compounds in the urine or the breath, without having contributed directly to their formation.

With regard to the fats, their action is complicated by the fact that they consist of two parts, fatty acid and glycerol. Glycerol belongs distinctly to the class of antiketogenic compounds, and its inhibitory action may be so great as to prevent any ketogenic action which the fatty-acid moiety may have. As to the fatty acids themselves, the results of feeding these substances to diabetics or persons in a state of inanition are not altogether in concordance. Joslin, taking into account the absorption of these substances by the intestinal wall, was unable to attribute to them a ketogenic function, and this was particularly true of palmitic and stearic acids. Oleic acid was ketogenic. His results are confirmed by Geelmuyden.

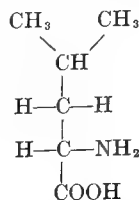
It is well known that when fatty acids or soaps are fed, the acids pass through the intestinal wall in the form of soaps, and are immediately synthesized to neutral fats, the glycerol for this purpose being supplied by the organism itself. Borchardt considers that the greater part of any ketogenic function which the fatty acids may have is due to the abstraction of this necessary amount of glycerol, and they, therefore, do not act as direct acetone formers. In a control of this statement, Waldvogel has injected olive oil under the skin, and found no increase in the acetone elimination, although when this substance is given by the mouth the acetonuria is increased. Absolutely neutral fats have been shown by Geelmuyden and by Hagenberg to decrease the formation of acetone. Hence, one must conclude that the greater part of the ketogenic action of fats, especially those of the higher fatty acids, is due to their content in free fatty acids, which in their resorption combine with the antiketogenic glycerol, and so remove it from its sphere of action.

As the chief source of the acetone compounds come the amino acids produced by the breaking down of protein substances. Between many of these compounds—leucin, arginin, serin, cystin, etc.—and β oxybutyric acid there is a very clear chemical relationship. Further it has been shown by Embden that the perfusion of blood containing leucin through the surviving liver results in a prompt increase in the amount of acetone in the blood. Baer and Blum fed leucin to diabetics and obtained an increase in the amount of acetone compounds in the urine. Borchardt fed protamines containing a large amount of arginin, and also obtained a decided increase of acetone in the urine. Other amino acids have been fed by Embden and Salomon with like results. These are tyrosin and phenylalanin. On the other hand, glycocoll, alanin, glutaminic acid, and asparagin when circulated through the liver did not increase the acetone content of the blood.

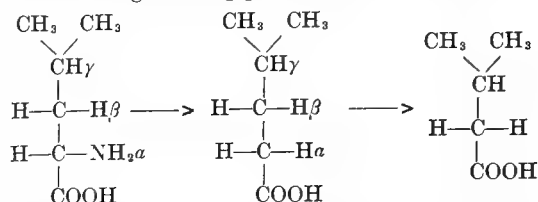
The laws which govern the formation of acetone from the substances above mentioned are chemically somewhat complicated, and even yet have not been completely worked out. They depend in part on the capacity of the organism to remove the amino group, and effect an oxidation at the β carbon atom (the atom

next that carbon atom to which is attached the terminal carboxyl-group). One example will serve perhaps to indicate the type of reaction which may occur.

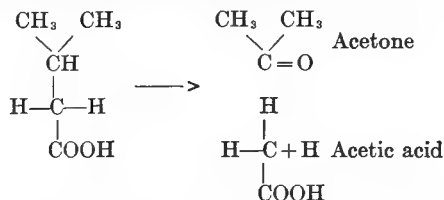
Leucin has the following formula:



By a simultaneous removal of the amino group, removal of CO_2 from the carboxyl group, and subsequent oxidation, one may have the following hypothetical series of changes taking place:



The final step here is isobutyric acid. If now this compound be oxidized at the β carbon atom, one obtains acetic acid and acetone as follows:



As the acetates are easily destroyed by combustion in the organism, the acetic acid formed in the reaction disappears, and acetone is left. Similar reactions may be made out for the other amino acids which produce acetone compounds. Arginin, one of the diamino acids, is markedly ketogenic, according to Borchardt, and therefore substances containing large amounts of protamines, and consequently arginin, such as thymus and roe, are to be avoided in cases of acidosis.

Reactions in which the β carbon atom is attacked by oxidation have been very completely studied by Knoop. By using compounds in which a straight chain of a fatty acid is linked to a benzene group, he was able to show that in every instance oxidation was effected at this place. The rule, therefore, seems to be a general one in the katabolism of fatty acids.

The question whether the fatty acids or proteins are the principal source of the acetone compounds is thus fairly well settled, for it is seen that with the proteins the intermediary metabolism must take place through steps involving the formation of a lower fatty acid.

Of very great importance from the standpoint of acidosis are the antiketoplastic substances. As has already been defined, these are the substances which prevent the excessive formation of acetone compounds, or reduce the amount which is excreted by the urine or the breath. As v. Noorden remarks, the extension of these substances is one of the most practical points in the therapy of diabetes.

Outside of the alkalies, such as sodium carbonate, or certain salts of easily oxidizable organic acids such as sodium citrate, the chief members of this group are the carbohydrates. Without exception, all carbohydrates have the property of decreasing the amount of acetone compounds, whether produced by starvation or by diabetes. Owing to the somewhat close similarity between these compounds and glycerol, the latter is next

in antiketogenic action. It is unfortunate, however, that its use in diabetes is attended with a marked increase in the amount of glucose eliminated. Another member of this class is alcohol. Neubauer has shown beyond question that alcohol diminished acidosis to a marked degree, and at the same time appeared to diminish the amount of sugar excreted.

Besides these, certain of the amino acids are quite antiketoplastic. Of these may be mentioned alanin and asparagin. The experiments with glycocoll and glutaminic acid were not altogether positive. It is worthy of note that Eppinger gave amino acids with what would have been fatal doses of inorganic acids, and was apparently able to effect recovery. His results, and the conclusions which he has drawn from his work, will, however, bear a control.

Basing his classification on the content of antiketogenic amino acids, Borchardt arranges the proteins in the following order: Protamin, histone, egg-albumin, pancreas, casein. Protamin gives the highest amount of acetone, while casein gives the least.

What the mechanism is whereby the carbohydrates and certain of the amino acids are able to effect a reduction in the excretion of acetone compounds, is absolutely unknown. One reason for this lack of knowledge is the incompleteness of our information regarding the normal intermediary metabolism of carbohydrates and of fats. These are two of the most difficult of the problems of biological chemistry. Waldvogel believes that the carbohydrates act by sparing the fats from combustion, but it has been shown repeatedly, and the present writer has confirmed the results, that only a very small quantity of sugar is needed in the marked acidosis accompanying the starvation of a case of pernicious vomiting of pregnancy, for example, to abolish all signs of acidosis from the urine, and this without in the least affecting the general condition of the patient. The amount of carbohydrate which is necessary to prevent the appearance of these compounds in the urine is even smaller than that used to abolish them, once they are present, and is by no means large enough to protect any very considerable quantity of body fat.

Nasse some years ago suggested a process of "secondary oxidation" of the fats as a result of the primary oxidation of the carbohydrates, and a somewhat similar idea has been put forward by Hirschfeld. None of these theories has any very definite experimental groundwork, and on the whole they are quite inadequate.

To sum up as briefly as possible what is known about the source of the acetone compounds, it may be said that the higher fats probably do not form acetone compounds. Some of the lower fats and fatty acids have this property. Certain of the amino acids are probably the chief source of these substances, and form them by losing the amino (NH_2) group, with the loss of carbon dioxide, and oxidation at the β carbon atom. Thus, in effect, the amino acids are transformed into lower fatty acids, which are changed to β oxybutyric acid and acetone.

Substances which give rise to glucose in the organism are antiketoplastic. The exception to this rule is alcohol, which apparently has the most useful property of diminishing the glucose and acetone bodies at the same time.

As in the combustion of proteins large amounts of sulphuric and phosphoric acids are formed, these also probably play a part in acidosis. Salkowski showed, many years ago, that the administration of taurin to rabbits was sufficient to produce enough sulphuric acid by oxidation to poison these animals. This was a case of endogenous acid intoxication from inorganic acids.

The Conditions under which Acidosis Takes Place.—In the healthy subject there is one condition which produces the elimination of acetone compounds; this is starvation. Not only complete inanition will bring about this anomaly, but the mere abstention of the in-

dividual from carbohydrates is almost equally effective. The length of the fast which is necessary is very short, less than twenty-four hours, and in all subsequent discussions of acidosis and the pathological significance of acetone compounds in the urine this fact must constantly be borne in mind. Indeed, a large amount of the clinical importance which has been attached to these compounds is rendered absolutely worthless when it is found that the observations have included no consideration of the condition of nutrition of the patient or of the amount and kind of nourishment which he consumed.

Abstention from food for twenty-four hours is usually sufficient to cause the appearance of acetone in the urine, so that it can be detected with Lieben's test. From the twenty-fourth to forty-eighth hour acetoacetic acid makes its appearance, and at the same time β oxybutyric acid may be detected. Under-nourishment for any length of time may also cause acetone to appear, especially if the supply of carbohydrates has been insufficient for the needs of the body. That simple starvation may produce a very considerable acidosis is shown by the recent work of Brugsch on the professional faster Succi. This person was a man with a very decided amount of body fat. During the twenty-fifth day of his fast he eliminated acetone compounds equivalent to 13.6 grams of β oxybutyric acid. Similarly Satta has shown that carbohydrate starvation alone may lead to an acidosis equivalent to 20.0 grams of oxybutyric acid. This is a degree of acidosis which would be considered high even in cases of diabetes. That all fasting subjects do not react with the same degree of acidosis is shown by a parallel case reported by Brugsch. This was a woman suffering from stricture of the oesophagus. She was in the very extreme of emaciation, as was shown at the autopsy, when it was found that even the plantar fat had disappeared. This patient excreted practically no acetone compounds. From these two observations Brugsch was led to conclude that the source of the acetone compounds was the abnormal metabolism of body fat. This is not the only conclusion which can be drawn from the results. It is also possible that the patient had adapted herself to an extraordinarily small caloric need, so that the amount of tissue which she consumed was adequate for her. Other observers have seen similar large amounts of acetone compounds appear during starvation. Nebelthau's case, in which 66 per cent. of the total nitrogen was eliminated as ammonia, must be included in this group.

Having shown that simple inanition may produce large amounts of acetone compounds in the urine, one is led to inquire which of the three classes of food-stuffs it is that the abstention from is most effective in causing the increased elimination of acetone compounds in the urine when it is withdrawn from the diet. As might be expected from their marked antiketogenic action, the carbohydrates, and they alone, are the substances whose withdrawal causes the features of acidosis. One cannot therefore speak of a starvation acidosis, but simply of a carbohydrate acidosis. The reason why, as a rule, one gets a less severe type of acidosis in carbohydrate inanition than in complete starvation is due largely to the antiketogenic constituents of the proteins, and to the glycerol content of the fats.

Pathological Acidoses.—There is possibly no one urinary diagnostic feature in clinical medicine which has been called upon to account for such a diversity of symptoms as the presence of acetone and its allied compounds. A partial list of the affections with which they have been associated is as follows: cyclic vomiting in children; vomiting in pregnancy; eclampsia; fetal death; post-operative intoxications, especially associated with narcosis; hyperthermia; pulmonary tuberculosis; malignant growths; asthma; toxic conditions following the use of antipyrin, morphine, atropine; carbon-monoxid poisoning, etc.

It will be noted that almost without exception the conditions are those in which undernutrition or short starvation is prominent. In the acetonuria following narcosis one is usually dealing with abstention from food for a period of time quite sufficient to provoke the appearance of acetone in the urine in healthy individuals.

What is of paramount importance in the consideration of these cases is a statement of the amount of the carbohydrate intake and of its resorption. It is quite possible, for example, in children with a severe gastrointestinal derangement, that sufficient carbohydrate may have been given to protect the child from an acidosis, but owing to the digestive disturbance the antiketoplastic substance is not resorbed, and so one has to do with simple carbohydrate starvation.

In a careful analysis of the clinical literature dealing with acetonuria in its relation to acid intoxication one is struck with the fact that little attention has been paid to this side of the question. Mohr, in his valuable review of diabetic and non-diabetic autointoxications with acids, has come to a similar conclusion, and is able to see in the acetonurias of these various conditions nothing but the acidosis resulting from an insufficient supply of carbohydrates. Special mention might be made of pernicious vomiting in pregnancy, because here the acidosis as revealed by the acetone compounds, and more especially by the relative amount of ammonia in the urine has been made a criterion whereby nervous vomiting might be distinguished from a more pernicious type. The present writer has criticised this view severely, and since that time his attitude has been supported by others who have had occasion to consider the subject. Certain it is that it is physiologically impossible to indicate operative interference in cases of pernicious vomiting in pregnancy from either an analysis of the urine for ammonia or an examination of the acetone-compound elimination.

The etiology of eclampsia has been the subject of numerous investigations in which the starting-point has been the view that acid intoxication plays a prominent part, and quite recently Zweifel has narrowed down the toxic agent to sarcolactic acid, which is found in the urine during and after the seizures. Dreyfus has repeated and confirmed Zweifel's results as to the presence of lactic acid in the urine, but is quite unable to find any etiological relationship between the appearance of the acid in the urine and the convulsions. It is altogether probable that lactic acid in the urine in eclampsia is the result of insufficient oxidation and increased muscular effort, and does not in any way figure as a cause of the convulsive seizures. It has been repeatedly found by Araki and others in the urine in cases of carbon-monoxide poisoning and other conditions where its formation certainly gave rise to no additional toxic effects.

Diabetic Acidosis.—When one comes to the consideration of diabetic acidosis one is confronted with a problem of singular complexity. Obviously one is dealing with a condition which is most favorable to the elimination of acetone compounds. There is in the first place the usual strict diet of fat and carbohydrate, which induces prompt acidosis in the normal subject; there is secondly the incapacity of the diabetic to utilize the carbohydrate which is formed in the body from protein, and possibly from fat. This incapacity is often so complete that on a strict diet containing only fat and protein, for every gram of nitrogen excreted the patient excretes 3.5 to 4.0 grams of sugar. One is not astonished, therefore, that a patient in this condition, rejecting unused the sum total of the antiketoplastic substances, excretes very large amounts of acetone compounds.

It is now important to decide whether this acidosis is merely a carbohydrate inanition effect, or has a specific quality not seen in the acidoses previously discussed. In so far as one may judge at present, one must acknowledge that diabetic acidosis presents features which seem to indicate a specific nature apart from the

influence of carbohydrates. The literature on the subject is extremely full, but v. Noorden has summed up the evidence in favor of its specific quality as follows.

1. Certain diabetics tolerating a diet containing 60 to 80 grams of carbohydrate eliminate no more acetone than a normal person on full diet. On transference to a carbohydrate-free diet the amount of acetone compounds increases, but finally on the same strict diet diminishes.

2. Others with moderately severe diabetes may eliminate, on a diet containing carbohydrate nearly to the limit of their tolerance, 1 gram or more of acetone. By transference to a strict diet the amount of acetone compounds increases, and continues to increase so long as the strict diet is adhered to.

3. In the third group, one may have individuals with certain characteristics of severe diabetes. They react favorably, so far as the disappearance of glucose from the urine on a strict diet is concerned; and yet under all circumstances they excrete large quantities of acetone compounds in the urine. In these cases one also gets marked variations in the amount of the acetone compounds excreted which have apparently no causal relation with the type of food administered. Von Noorden mentions a case in which 50 to 60 grams of β oxybutyric acid were excreted daily over a very long period of time. Further, there are marked individual differences in the way patients react with the same amounts and qualities of food. From these considerations one is forced to the conclusion that the acidosis of diabetes is not entirely due to carbohydrate inanition.

Acid Intoxication.—While there can be no doubt as to the nature and severity of an acidosis due either to carbohydrate inanition or to diabetes, the matter is not quite so clear when one comes to connect the appearance of the acetone compounds in the urine with definite toxic effects.

Each of the compounds in this series has in its turn been the subject of numerous investigations as to its toxicity. Twenty grams of acetone produce some drowsiness in a man. The injection of 1 gram of acetone hypodermically had no effect whatever in the general condition of a girl. According to v. Jaksch, acetoacetic acid is not toxic, and even doses as large as a gram have been given to a frog without the slightest effect. The results with β oxybutyric acid agree in most respects with what v. Jaksch obtained with acetoacetic acid. Most of the experiments, it is true, have been performed with the inactive acid, while the acid formed in the organism is the levorotatory modification. Schwarz was, however, unable to produce any toxic symptoms with 8 grams of the active acid when given to a dog. Wilbur, working in v. Noorden's laboratory, has apparently obtained some slight degree of toxicity with the active acid. Very recently Desgrez and Saggio have claimed that both acetoacetic acid and β oxybutyric acid are toxic and cause a "demineralization" of the organism. The results of the French authors do not appear to be well enough founded to deserve serious consideration.

So far as positive evidence is concerned, we have little of direct value to indicate that the toxemia which leads to diabetic coma, or, as Naunyn insists it should be called, dyspnoeic coma, is an intoxication produced by acid products. Nevertheless, the opinion in favor of an acid origin is so universal, and there is so little to supplant it, that one must admit a weight of *opinion* in place of a weight of *evidence*. The reasons for viewing dyspnoeic coma as an acid intoxication are as follows, and are given very completely by Naunyn in his work on diabetes.

In the onset of coma, the percentage of carbon dioxide in the blood falls markedly below the normal 30 to 40 volumes per cent. This indicates that the amount of carbonates present in the blood, by which the carbon dioxide is transported from the other tissues to the lungs, has decreased. It has also been shown that preceding the coma there is usually a marked rise

in the amount of acids, both acetoacetic and oxybutyric, but this is not always the case; for numerous cases of coma are on record in which the amounts of these substances were lower at the time of the attack than for long periods previously. Further, the sudden change from a mixed diet to one containing fat and protein only has often provoked serious symptoms, which Naunyn believes are due to the flooding of the organism with acid products both of inorganic (sulphuric and phosphoric) and organic character. The clinical observations, too, on the use of sodium carbonate in preventing the onset of coma have many features which cannot be ignored, and lead one to believe that this type of therapy is of very real value. As much cannot be said for the use of carbonates during the coma itself. Here the reports which can be relied upon are almost hopelessly unfavorable.

One point which has been suggested by some authors as to the relation between the acid products appearing in the urine and the onset of the coma seems worthy of notice. It is quite possible that there is no definite relation between the urinary products and the onset of the attack, for the reason that it is not the amount of acids which appear in the urine which conditions the coma, but the amount which is retained by the tissues. This would explain why cases such as v. Noorden's excreted large amounts of acid in the urine without having any symptoms of acid intoxication. The products were eliminated as quickly as they were formed. On the other hand, a patient might form quantities of acids which would not be eliminated, and that which was retained might exert its toxic effect. In explanation of the inefficacy of the sodium carbonate treatment, it has been urged that the alkali circulates in the fluids which bathe the cells, but does not actually reach those intimate cell structures where the toxic action of the acids is exerted.

The most critical analysis of the theory of acid intoxication has recently appeared from Tangl's laboratory. Two of his pupils, Szili and Benedict, have undertaken to compare the findings obtained in intoxication with inorganic acids with those got in diabetes. Szili made a careful study of the effects of inorganic acids on rabbits, dogs, and goats. These animals were injected with solutions of acids, and analyses made of the blood by titration, and by the estimation of the true reaction of the blood by means of gas-chain cells. It was found that with lethal doses of acids the blood had a lower concentration of hydroxyl ions than distilled water; that is to say, the blood, compared with distilled water, had actually become acid. At the same time, however, it reacted alkaline to lacmoid paper. Of extreme importance in this series of experiments was the fact that it was possible to bring the animals immediately from a state of dyspnoic coma by the intravenous injection of solutions of sodium carbonate. As a result of this work Benedict undertook a study of diabetic coma, following the methods employed by Szili.

He sums up the reasons which have been given for believing that diabetic coma is the result of poisoning by acids as follows:

1. Severe diabetics produce, besides the normal acid products of metabolism, excessively large amounts of organic acids.

2. The fixed alkalies, sodium, potassium, calcium, and magnesium, are not sufficient to combine with the continual excess of acids produced, and hence large quantities of ammonia are used for this purpose.

3. As increased acid production and increased ammonia elimination almost always precede the onset of dyspnoic coma, and as β oxybutyric acid is not toxic in itself, one must assume that the toxemia is due to the acid character of the compounds when the amount of alkali formed is not sufficient for their neutralization. (a) The similarity between the coma produced by inorganic acids and the dyspnoic coma of diabetes has long been recognized. (b) Blood investigations of

diabetics have led to the assumption of a decreased alkalinity of the fluid. The carbon dioxide content is lowered even to 4 volumes per cent. instead of the normal 30 to 40 volumes per cent.

The points which stand in the way of believing that diabetic coma is an acid intoxication are the following:

1. Between the dyspnoic coma and acid intoxication by inorganic acids there is a fundamental difference which can scarcely be explained away. While animals poisoned by inorganic acids may be made to recover almost immediately by the intravenous injection of alkalies, this is practically never the case in the coma of diabetes.

2. It appears impossible to define accurately a diabetic coma. One often finds cases of carcinoma, inanition, or hepatic disease in which the terminal coma has all the clinical signs of diabetic coma.

3. The assumption of an acidification of the tissues rests on the finding of a diminished carbon-dioxide content of the blood; but one finds a similar decrease in this value in other conditions without coma intervening. On the other hand, cases of coma in diabetes are on record in which the carbon-dioxide content of the blood was scarcely below the normal.

In a control of these differences, Benedict investigated the actual reaction of the blood in cases of diabetes by means of the gas-chain cell. The amount of titratable alkali was also estimated. Eleven cases of diabetes were examined, of which three terminated fatally in coma. In the three cases of coma the concentration of hydroxyl ions in the blood was from 0.99×10^{-7} to 0.42×10^{-7} , with an average value of 0.74×10^{-7} . In normal subjects there is a variation from 4.1×10^{-7} to 0.41×10^{-7} . So that in all cases the reaction was alkaline within what has been found to be normal limits. It has also been shown that in other conditions, e.g., pregnancy, the alkalinity may fall to 0.2×10^{-7} without any danger to life. He therefore believes that neither the results of Szili nor his own investigations lend any support to the view that the dyspnoic coma of diabetes is due to an intoxication by acids.

Folin doubts that the evidence presented by Szili and by Benedict is sufficient to discredit the acid-intoxication theory, and bases his conclusions on the fact that the Hungarian investigators have viewed the intoxication from the standpoint of the physical reaction of the blood, and that poisoning with large amounts of acids does not yield comparable results with the slow toxemia resulting from the production of an excessive amount of acid in daily metabolism.

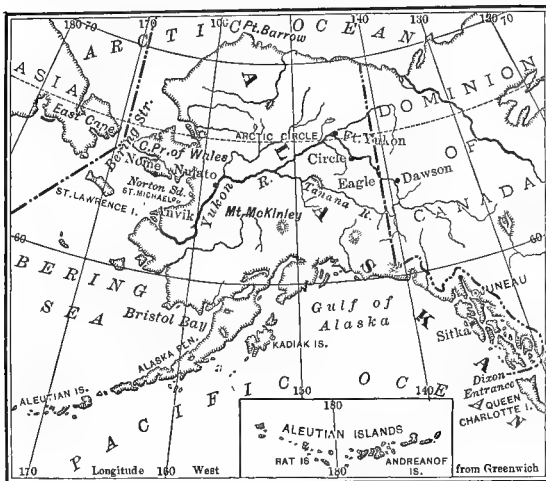
While the latter point is certainly well taken, the present writer cannot agree that the former criticism is justified. The acid effects of solutions of acids are due solely to the concentration of hydrogen ions. If the effects of the organic acids produced in the abnormal metabolism of diabetes are not those of hydrogen ions, one must assign a name other than acid intoxication to the toxemia resulting from their action in the organism.

C. G. L. Wolf.

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The climate of temperate Alaska is characterized by two striking peculiarities: comparative warmth and great moisture, caused by the Kuro Siwo, the "Gulf Stream" of the Pacific. This current crosses the Pacific in about latitude 45° N., and impinges on the coast of British Columbia where it divides, one portion turning northward and westward and the other southward. As a result of this condition, the temperature is greatly modified from what the latitude alone would lead one to



The second peculiarity of temperate Alaska is moisture in the form of rain or fog, and in the Sitka division, which extends from Dixon Entrance to William's Sound, the yearly rainfall is from eighty to one hundred and three inches, and there are on an average but sixty-six clear days in the year. "When the sun shines, the atmosphere is remarkably clear, the scenic effects are magnificent, all nature seems to be in holiday attire. But the scene may change very quickly; the sky becomes overcast; the winds increase in force; rain begins to fall; the evergreens sigh ominously, and utter desolation and loneliness prevail." [United States Department of Agriculture, Weather Bureau.] The Sitka district is very mountainous, and the coast bold and steep with few beaches. The mountain sides are densely wooded, and the snow line begins at an elevation of from three thousand to five thousand feet. The prevailing winds being westerly and off the ocean, bring the moisture to the snowy mountains, which condense it. Hence it is the combination of the mountains, the prevailing moist winds from the sea, and the warm Japan current, which results in this enormous rainfall, nowhere else equalled in the United States, the annual rainfall at Sitka being more than double that on the Atlantic coast. At Sitka the rainfall for the three winter months is about thirty inches, and for the three summer months sixteen inches.

The country is heavily wooded with spruce, hemlock, and cedar, and the vegetation is dense. On account of the sparse sunshine agriculture is difficult, but many garden vegetables are successfully grown.

In the Kadiak district, which comprises Cook's Inlet, the peninsula of Alaska, and the Kadiak Islands, the climate is similar to that of the Sitka region, but there is more sunshine and less rain, and the seasonal extremes of temperature are greater. At Kadiak the annual mean temperature is 40.6° F., and the number of days of rain or snow for ten months of the year 1899 was 133, and the number of cloudy days 124, making 257 cloudy and rainy days out of 304. The monthly mean temperature at Kadiak for eight years is as follows:

January.....	30.0	August.....	55.2
February.....	28.2	September.....	50.0
March.....	32.6	October.....	42.3
April.....	36.3	November.....	34.7
May.....	43.2	December.....	30.5
June.....	48.5	Year.....	40.6
July.....	54.7		

UNALASKA—LAT. 53° 54'; LONG. 166° 24'. MONTHLY MEAN TEMPERATURE (DEGREES FAHRENHEIT) FOR SIX YEARS.

January.....	30.0	August.....	51.9
February.....	31.9	September.....	45.5
March.....	30.4	October.....	37.6
April.....	35.6	November.....	33.6
May.....	40.9	December.....	30.1
June.....	46.3	Year.....	38.7
July.....	50.6		

	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.
Juneau—												
Mean maximum.....	41.7°	43.0°	50.7°	57.2°	66.2°	73.2°	78.5°	67.7°	63.7°	58.7°	49.6°	47.6°
Mean minimum.....	9.5	12.0	6.0	29.5	38.2	39.2	44.0	41.7	35.7	27.0	19.3	11.0
Daily mean.....	29.7	29.1	32.8	40.6	46.6	56.6	57.5	54.2	49.8	43.0	35.9	32.6
Sitka—												
Mean maximum.....	51.0	47.3	53.6	58.0	64.7	67.7	78.5	65.2	65.0	60.0	54.0	49.7
Mean minimum.....	23.3	16.3	7.6	28.3	31.2	34.7	40.0	39.7	37.7	30.5	23.3	21.3
Daily mean.....	35.7	34.3	35.8	42.0	44.0	50.6	55.5	54.4	50.9	45.2	38.0	34.3

According to Harriman (Alaskan expedition), there were at Unalaska only 8 days in the year, during several years' record, which were entirely clear, the remaining 313 being cloudy and 271 of these were rainy or snowy.

The Yukon district, or Northern Alaska, comprises that vast region of the Yukon Valley which extends from the Alaskan Mountains to the Arctic Ocean on the north and Behring Sea and Strait in the west.

In the interior of this region the climate becomes colder and drier—extremely rigorous during the long winter and relatively hot in the short summer. As one continues north arctic conditions of climate begin. On the Behring Sea coast, north of the Aleutians Islands, the winter climate is much more severe than that of temperate Alaska on the Pacific coast, but in summer the difference is less marked. At St. Michaels, on the south side of Norton Sound, the mean summer temperature is 50° F., which is but 4° below that of Sitka; and at Point Barrow, on the Arctic Ocean, the most northerly point in the United States, the mean summer temperature is 36.8° F. Furthermore, the winter on the Behring Sea coast about the mouth of the Yukon River and the Seaward Peninsula is somewhat less protracted and severe than in the interior, although it is still long, and from October to May the temperature rarely rises above the freezing point.

Extreme cold, however, as one knows from the experience of Arctic explorers, is not detrimental to health, and at Nome, the most populous mining town in Alaska, the winter is said to be the most agreeable season of the year, in spite of the fact that in midwinter there are but few hours of daylight, the shortest days giving but about three and a half hours of dusky light. "With hands and feet warmly protected, and winter underwear and wind-proof outer clothes *and exercise*, one can comfortably weather a degree of cold which, in lower latitudes, would immediately transform him to an icicle. This is due to the dryness of the cold." ("The Land of Nome," by Laurie McKee, New York, 1902.)

The following table, compiled from observations of the United States Weather Bureau, gives the annual and

September or 1st of October. The prevailing winds are from the north, and severe blizzards with strong north-east gales are frequent in winter. In comparing the climate of Nome with that of the Klondike region to be spoken of directly, it may be said that in general the climate of the latter is rather more favorable than that of the former. The most trying climatic element is the continual wind.

Fifteen hundred miles in the interior, to the east of Nome City, is the Klondike region, also famed and frequented for the gold discovered there. It is reached either overland—the common passenger route from Skagway by rail for about one hundred miles by the White Pass and Yukon Railroad, and thence by steamer on the upper Yukon to Dawson—or by the longer all-water route, which is principally used for freight, by way of the lower Yukon. The distance from Skagway to Dawson, the principal city of the Klondike (in Canadian Territory), is five hundred and eighty miles.

The general characteristics of the Klondike climate are similar to those of Nome—long, extremely cold winters, with much snow and "brief but relatively hot summers." "In midwinter the sun rises from 9:30 to 10 A.M., and sets from 2 to 3 P.M., the total length of daylight being about four hours." (United States Weather Bureau report.) In June the sun rises about 1:30 in the morning and sets at 10:30 P.M., "giving about twenty hours of daylight, and diffuse twilight the remainder of the time." "During the warmer days of summer the heat feels almost tropical; the winter cold is, on the other hand, of almost the extreme Siberian region." "Yet a beautiful vegetation smiles not only over the valleys, but on the hilltops, the birds gambol in the thickets, and the tiny mosquito pipes out its daily sustenance to the wrath of man." (Heilprin, "Alaska and the Klondike.")

The following observations of mean and extreme temperatures of the United States Weather Bureau made at the Yukon River at the international boundary, about eighty miles north of Dawson, from September, 1889, to June, 1891, will indicate approximately the temperature conditions of the Klondike.

ST. MICHAELS.

	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Year.
Mean maximum (degs. Fahr.)	33.5°	38.0°	32.0°	40.5°	48.5°	62.5°	77.0°	65.0°	56.0°	47.5°	37.0°	34.0°
Mean minimum.....	-34.0	-20.0	-17.0	-20.5	-7.0	27.0	40.0	37.0	25.0	6.5	-4.0	-24.0
Mean monthly.....	-8.0	-2.3	8.9	19.9	33.1	46.3	53.6	51.9	43.9	30.5	15.6	4.8	26.1°
Extreme maximum.....	44.0	41.0	43.0	46.0	57.0	75.0	75.0	69.0	69.0	54.0	42.0	45.0	75.0
Extreme minimum.....	-47.0	-41.0	-39.0	-27.0	-2.0	22.0	33.0	32.0	18.0	3.0	-24.0	-43.0	-47.0
Mean number of rainy and snowy days.....	7	4	6	8	9	9	12	14	14	11	9	5	108

monthly mean temperatures and the extremes for St. Michaels, which is on the southern side of Norton Sound; it also may be utilized for ascertaining approximately the yearly temperature of Cape Nome, which is one hundred and fifty miles distant on the northern shore of Norton Sound, at its junction with Behring Sea. In the same table will be found a statement of the mean number of rainy and snowy days. As will be seen, the rainfall is very light, and is about fourteen inches annually, a striking contrast to that of Southern Alaska.

From observations made on the Yukon, not far from the site of the gold discoveries, by the United States Coast and Geodetic Survey for a series of six months, the following temperatures are noted: From October, 1889, to April, 1890, the mean temperature was as follows: October, 33° (above zero); November, 8° (above zero); December, 11° (below zero); January, 17° (below zero); February, 15° (below zero); March, 6° (above zero); April, 20° (above zero). "The daily mean temperature fell and remained below the freezing point (32° F.) from

YUKON RIVER AT INTERNATIONAL BOUNDARY, LAT. 65°, LONG. 141°.

	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Year.
Mean temperature (degs. Fahr.)	-17.0°	-10.0°	7.0°	24.0°	45.0°	57.0°	60.0°	52.0°	39.0°	31.0°	3.0°	-16.0°	23.0°
Extreme maximum.....	25.0	37.0	38.0	56.0	74.0	84.0	87.0	74.0	66.0	52.0	39.0	17.0	87.0
Extreme minimum.....	-60.0	-55.0	-45.0	-26.0	8.0	30.0	35.0	31.0	14.0	4.0	-35.0	-49.0	-60.0

One cannot be sure of reaching Nome by sea much before the middle of June on account of the ice in Behring Sea, or of getting away from there after the latter part of

November 4th, 1889, to April 21st, 1890, thus giving one hundred and sixty-eight days as the length of the closed season. The lowest temperatures registered dur-

ing the winter were: 32° below zero in November; 47° below zero in December; 59° below zero in January; 55° below zero in February; 45° below zero in March; 26° below zero in April. "The greatest continued cold occurred in February, 1890, when the daily mean for five consecutive days was 47° below zero. The weather moderated slightly about the 1st of March, but the temperature still remained below the freezing point. Generally cloudy weather prevailed, there being but three consecutive days, in any month, with clear weather, during the whole winter. Snow fell upon one-third of the days in winter, and a less number in the early spring and late fall months. The change of temperature from winter to summer is rapid owing to the great increase in the length of the day." (Bulletin of the United States Weather Bureau, July 29th, 1897.)

Harriman (Alaska expedition) says that the mean temperature of the warmest month on the Yukon, in latitude 64° 41', was 4° higher than at Sitka over five hundred miles farther south; but while at Sitka the extreme range of temperature is 90°, it will be seen from the above table that on the Yukon it is 147°.

"With a claim to have seen many distant lands," says Professor Heilprin, "I can truthfully say that never before had it been my fortune to experience such a succession of wonderful summer days as during my stay in the region about Dawson. From August 6th to September 20th, barring three days of partial rain, and perhaps a fourth of cloudiness and mist, the weather was simply perfection—a genial, steady, mild summer, with a temperature rising at its highest to about 80° or 82° F. in the shade."

The average annual rainfall is given as from ten to twenty-five inches, and, according to the authority just quoted, the weather is bright and sunny, and there is practically no fog. "There is more sunshine," says Harriman, "in a month (in the interior) than at Sitka in a year."

Such a climate, although severe, is said to be a healthy and invigorating one to most people, for the cold is uniform and dry, and there is very little wind, a contrast, in this respect, to Nome. In a report by Capt. W. P. Richardson, Eighth Infantry, U. S. A., the fact is stated that when the thermometer rises to zero, as it sometimes does in midwinter, it is too warm for comfortable travel. The best temperature, he states, is from 10° to 25° or 30° below zero. "With this temperature the sleds run easily, dogs work with spirit, and one can exercise with the warm clothing necessary at all times in Alaska without discomfort." The ground is frozen deeply, and in the warmest season only thaws to the depth of a foot or two.

The vegetation in the Klondike region is, comparatively speaking, far more luxuriant than at Nome, where it is of arctic character, chiefly mosses and lichens, and the tundra or thick peat moss, or grass which renders foot travelling wearisome and slow. In the Klondike region the country is well wooded, principally with the spruce, although the aspen, birch, balsam, and poplar are found, and this region of forest extends with breaks several hundred miles northward of Dawson. In the summer the country is green and variegated, with a rich flora. Grass grows abundantly, and all the hardy vegetables are said to grow without trouble. Grain, vegetables, and fruit have been raised in small quantities. The native strawberry is found in many parts of the Yukon valley, and so also are various native berries, especially the blueberry. In the Yukon valley, near Dawson, celery, lettuce, potatoes, turnips, etc., have been successfully grown, as well as oats and wheat, and this in a latitude which runs through Greenland and Iceland! Of course such results would be impossible were it not for the fact that the summer days, though few, are very hot and the sun is almost continually above the horizon.

Fish, furs, and gold are the principal industries of Alaska. The discovery of gold has naturally attracted the most attention, but the fisheries form one of the most important industries, and next in importance to the fur trade is the salmon industry. The population was 63,592

at the census of 1900, of which number over 45,000 were males and about half were whites.

Nome City is the largest town, with a population of over 12,000, and next comes Skagway, with a little over 3,000. Dawson, the principal town of the Klondike region, in Canadian Territory, had in 1899 16,000 inhabitants.

The testimony is somewhat conflicting regarding the mosquitoes, but they are apparently pretty abundant, and at certain times and places constitute a veritable scourge. The gnats are also very annoying.

The accommodations, especially in the mining towns, are naturally not of the best, and are expensive; still, any one possessed of robust health need not be deterred either by the climate or by the poor accommodations from a journey to, or a permanent abode in, Alaska. The steamer accommodations from San Francisco, Seattle, or Vancouver are by some lines quite satisfactory. A summer excursion to the southeastern coast of Alaska—the icebergs region—is a favorite one.

References.—Various government reports from the Interior Department; Department of Commerce and Labor; Department of Agriculture, and the Weather Bureau; yearly reports of the governor of Alaska; Harriman, "Alaska Expedition"; Heilprin's "Alaska and the Klondike"; "The Land of Nome," by Laurie McKee; "The Pacific Coast Pilot," and many other special works.

Edward O. Otis.

ALYPIN is the benzoyl-ethyl-tetramethyldiaminopropanol hydrochloride $(\text{CH}_3)_2\text{N} \cdot \text{CH}_2 \cdot \text{C}(\text{C}_6\text{H}_5): (\text{C}_6\text{H}_5\text{COO}) \cdot \text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$. It occurs as a white crystalline powder, melting at 169° C. (336° + F.). It is highly hygroscopic and consequently very freely soluble in water and alcohol. Aqueous solutions are neutral and not changed to turbid appearance on the addition of a small quantity of sodium bicarbonate. Solutions may be sterilized by boiling for a brief period; if heat is continued, however, the alypin is decomposed. It has a strong, bitter taste.

Because of its hygroscopic nature, alypin should be kept in securely stoppered vials to exclude the air. From two- to four-per-cent. solutions are stable; weaker ones soon become mouldy. Potassium iodide T.S. produces a white precipitate; potassium dichromate T.S., a yellow crystalline precipitate which is soluble in hydrochloric acid; potassium permanganate T.S., a violet crystalline precipitate which becomes brown on standing.

Alypin is one of the many local anæsthetics which have recently appeared as surrogates for cocaine. It is claimed to equal cocaine in intensity and duration of anæsthesia; that its use does not affect the accommodation, produce mydriasis or intraocular pressure, and that it is less toxic than cocaine. Injections are followed by a transient hyperæmia. Reports do not agree as to the action of alypin upon the tissues; irritation, even necrosis, having been noted following its employment. Others claim it less efficient than cocaine.

In intralaryngeal intervention alypin seems to be an ideal substitute for cocaine. It is used externally to the unbroken skin or mucous membrane as well as hypodermically and subcutaneously. Indications for its use are the same as for cocaine. Solutions should be freshly prepared and may be combined with any one of the suprarenal principles—suprarenalin, adrenalin, or suprarénin. Locally alypin is used in ten-per-cent. solutions; hypodermically, one- to four-per-cent.; instillations into the eye, one- to two-per-cent.

Alypin nitrate may be combined with silver nitrate when treating urethritis or cystitis and to anæsthetize the urethra before the introduction of instruments.

ANÆSTHESIA, ELECTRIC.—Electric sleep or electric anæsthesia may be induced in man or in animals by means of the Leduc current—a direct current interrupted a given number of times per second—by means of a special interrupter designed by Professor Rouxéau,

of Nantes, France. The interrupter is known as the Leduc interrupter.

Instruments Needed.—A reducer of potential, a Leduc interrupter, a milliamperemeter, a mercury interrupter commonly used in laboratories, and a voltmeter.

The essential part of the Leduc interrupter is a wheel made of metal into which are inserted segments of stone or ivory, so that the electric current that passes through this wheel is interrupted at each stone segment. Two metal levers, one of which is movable, are in contact with the circumference of the wheel. The current passes through the interrupter when each of the two levers is in contact with a corresponding metal segment of the wheel; and the current is interrupted when one of the metal levers passes over a stone segment while the wheel is in motion. The period of the passage of the current is regulated by changing the position of the movable lever—while it is in contact with a metal segment of the wheel—in relation to the immovable lever, which is also in contact with a metal segment of the wheel. A scheme of the wheel and the relative positions of the levers is published in my Paris thesis, 1906.¹ A dynamo in the interrupter is run on a sufficient voltage to cause the required number of interruptions per second. The number of interruptions most favorable to the production of electric sleep or electric anæsthesia is one hundred and ten per second, and the most favorable period of the passage of the current is one-tenth. The new model of the Leduc interrupter is made by two different firms in Paris; a tachymeter shows the exact number of interruptions per second, and the period of the passage of the current is indicated on a scale connected with the movable lever. The number of interruptions per second and the period of the passage of the current should be regulated before the operation is begun.

Electric Sources.—My comparative studies of various electric sources lead me to believe that the tranquillity of electric sleep depends on the stability of the electric current used (see my paper "Electric Sleep," etc., published in the *Journal of Mental Pathology*,² and my thesis cited above). I discovered the fact that accumulators were preferable to the city current while I was experimenting in Rome, Italy, where the city current is an alternating current, and I was obliged to use accumulators.

The potential of the current should be limited to a little over the potential needed for the production of sleep. This precaution is particularly important when the operator has not had sufficient experience in the administration of electric sleep. One colleague, who is an accomplished physicist, electrician, as well as surgeon, electrocuted an animal instantly while trying to subject it to electric sleep before an audience of physicians assembled to witness the induction of electric anæsthesia. A small source of electricity makes it impossible to commit the error of electrocuting a subject instead of submitting it to electric sleep.

While experimenting in Rome, I also discovered that electric sleep was more quiet when the dynamo of the interrupter was run by a separate source of electricity.

Mode of Procedure.—The negative pole of electric source is connected with the reducer of potential, the Leduc interrupter, and the head electrode. The positive pole of the electric source is connected with the reducer of potential, the milliamperemeter, the small mercury interrupter, and the electrode at the lower part of the spine. The animal's fur is closely cut with scissors on the head and at the lower part of the spine, where the electrodes should be applied. Care should be taken not to inflict any cuts on the skin while the fur is being shaven. The shaven skin and the electrodes are thoroughly wet with a normal salt solution before the electrodes are applied.

The circuit is closed by means of the mercury interrupter, and the current is allowed gradually to course through the animal's body by shifting the handle of the

reducer of potential. As the voltage is being increased, the animal shows signs of uneasiness and tries with its forepaws to dislodge the electrode on the head, or makes an attempt to escape. But as the voltage is still further increased, the animal falls on its side, its body and limbs showing a generalized tremor. This tremor disappears as soon as the proper potential is reached, from five to ten volts, as indicated by the voltmeter placed in derivation. At this time the milliamperemeter registers from 1.5 to 3 milliamperes (the potential and tension for experiments on dogs and rabbits).

Limitations of the Degree of Electric Sleep or Electric Anæsthesia.—Electric sleep may be induced with a given voltage—five to ten volts for dogs of all sizes. If this potential is reduced by one or two volts, the animal resumes its defensive movements; if the potential is increased by one or two volts, breathing becomes difficult and the animal is thrown into a convulsive state that can be relieved only by reducing the potential. This peculiarity of reaction serves as a safeguard to the experienced operator; for the latter this reaction makes it impossible to commit the error of asphyxiating the animal instead of subjecting it to electric sleep. An "experienced operator" is a physician who has had not less than two years' daily experience in producing electric sleep, as well as in handling the instruments and the electric sources.

Mode of Reaction During Electric Sleep.—While under the influence of electric sleep the animal appears as follows: It lies on its side with its eyes open and the pupils slightly contracted. The forepaws are stiff, stretched out forward, and animated by a continuous fine tremor. The skin reflexes are exaggerated, but sensibility to pain seems to be abolished. The latter condition has made it possible for me to utilize electric anæsthesia in laboratory surgery practised on animals.

Electric sleep causes evacuation of the bowels, involuntary urination, and in pregnant animals it induces abortion.

Electric anæsthesia is never absolute in the sense that we understand the term chloroform or ether anæsthesia; during electric sleep an animal is very apt to lift its head, cry out, make some defensive movements, and then fall back on its side and remain quiet again for some time. If the animal keeps up its agitation, quiet may be restored by shifting the handle of the reducer of potential so as to decrease or increase the voltage by a fraction of one volt—one-tenth to one-half—according to the requirements. As soon as the circuit is opened, the animal wakes up. There are no after-effects.

Electric Sleep in Man.—Professors Rouxeau and Malherbe, of Nantes, were the first physicians to induce electric sleep in man, Professor Leduc having submitted himself under their care to this mode of producing anæsthesia, which he had discovered.³ In my thesis cited above may be found a full account of the sensations experienced by the subject during this sleep. Broadly speaking, there was complete inhibition of the cerebral centres of speech and of motility, and partial inhibition of ideation and sensibility. Professor Leduc says that at first he felt contraction of the muscles of his face and the limbs; there was a sensation of tingling in the fingers and toes; then he became unable to speak and finally he was completely unable to move or to react even to the most painful excitations. His throat emitted some noise, but this did not correspond to any sensation of pain; he thinks that the noise was caused by successive contractions of the laryngeal muscles. He experienced some difficulty in breathing. When touched, pricked, or pinched by his colleagues, he felt the tests, but the sensations were blunt—similar to those felt in a limb that is "asleep." The most painful sensation was the realization that there was taking place a successive dissociation and disappearance of his faculties. This sensation he likens to that experienced during a nightmare—when one dreams of being confronted by great danger, while he feels unable to move or to cry out for help. The experiment was re-

peated twice, for a period of twenty minutes each time. The potential measured thirty-five volts, registering four milliamperes. This voltage was not sufficient to cause the maximum degree of electric sleep, but the operators did not wish to risk using a higher voltage. Awakening took place as soon as the circuit was opened. There were no after-effects.

Cardiac Action, Blood Pressure, and Respiration During Electric Sleep.—Professor Rouxeau⁴ was the first physician to put electric sleep on a physiological basis. His researches show that during electric sleep the heart action remains normal, the blood pressure is slightly increased, and the respiration is slightly accelerated.

Temperature During Electric Sleep.—I was the first to study the temperature, cardiac action, and respiration during electric sleep prolonged for eight hours and twenty minutes. The respiration and cardiac action remained as was indicated above; the temperature remained normal or slightly below normal. Immobilization of the animal during that time is probably the cause of the slight fall of the temperature. For details of the case see my thesis¹ cited above.

Influence of the Electrodes.—The cathode should always be at the head. If the anode is applied at the head there is difficulty in breathing, and death may take place after two hours of electric sleep.

Practical Utility of Electric Anæsthesia.—Thus far I have been the only one to apply and utilize electric anæsthesia in laboratory surgery on animals. For the last two years I have used this form of anæsthesia instead of chloroform or ether. Under the latter anæsthetics death takes place after a period of two hours, whereas electric anæsthesia may be kept up for many hours without leaving any after-effects.

The operations I generally perform on dogs under the influence of electric anæsthesia are trephining of the skull, abdominal section, exposure of the carotid artery, etc. I have never lost any animal from the effects of electric anæsthesia. The mortality from chloroform or other anæsthesia is considerable among animals.

Inconvenience of Using Electric Anæsthesia.—The operator's hands are in the electric circuit while he operates on animals under the influence of electric anæsthesia. And the operator's whole body is in the circuit while thus operating in a room with a tile floor. The animal is disturbed every time the operator takes one of his hands out of the circuit. And while operating, the surgeon experiences a tingling sensation in his fingers. If a small voltage is used, the tingling is insignificant. But a large voltage, such as would be necessary to use for causing central anæsthesia in man, might become a great drawback during major operations requiring delicate handling. A rubber sheet spread out under the operator's feet and rubber gloves on his hands may help to do away with the inconvenience. But these details should be studied before passing any opinions on them.

Local Electric Anæsthesia.—Local electric anæsthesia may be produced in any part of the body by putting it into the circuit of the Leduc electric current. I have had local anæsthesia produced in my forearm by the application of one electrode at the elbow joint and the other at the wrist. A more practical application of the Leduc current than is the one considered in this paper is presented in my four papers published in the *Journal of Mental Pathology*.⁵ Louise G. Robinovitch.

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² Robinovitch, Louise G.: *Electric Sleep*, *Journal of Mental Pathology*, vol. vii., No. 4, 1906.

³ Rouxeau, Leduc et Malherbe: *Production de l'inhibition cérébrale chez l'homme par les courants électriques*. Société de Biologie, November 22d, 1902.

⁴ Rouxeau et Leduc: *Du temps pendant lequel peut être maintenu l'état de sommeil électrique*. Société de Biologie, July 4th, 1903.

⁵ Robinovitch, Louise G.: *Journal of Mental Pathology*, vol. viii., No. 3, 1907.

ANÆSTHESIA, RECTAL ETHÉRIZATION.—Etherization by rectum was first suggested by Roux in the *Journal de l'Académie des Sciences* in 1847. In the same year Pirogoff practised the method on the human subject. Duprey and a few others also tried it, but in general very little attention was given to it. However, after Mollière in 1884 revived the idea and spoke well of it, more attention was given to the subject. R. Weir, W. T. Bull, and others used it in New York and reported some good results, but in a few of their patients no anæsthesia was produced, while in others bad after-effects were observed; thus eight out of seventeen of Bull's patients developed melena and diarrhœa, and a few profound stupor with cyanosis. Weir lost an eight-months-old baby upon whom he operated for hare-lip; it died of melena twenty-four hours after operation. After 1884 nothing further was heard of the method until J. H. Cunningham, of Boston, brought it before the profession in 1898, since which time it has also been taken up again in France. Cunningham has reported forty-one cases; in seventeen the anæsthesia was first started by mouth, and in twenty-four the rectum was alone used. All the cases pointed to the practicability of rectal anæsthesia if properly administered. He obtained a good anæsthesia in all the patients, with no deaths, no diarrhœa, and no bloody stools. Leggett tried it at Roosevelt Hospital, New York, in 1907, in thirty-one cases, with no deaths; bloody stools once; unsuccessful anæsthesia three times.

Method.—Roux and Pirogoff used liquid ether mixed with water. Mollière, Bull, Weir, and the others of their time used vapor obtained by boiling ether at 122° F., the gas forcing itself into the rectum by its own expansion. By the latter method one could not appreciate the amount of ether used, and the vapor going over at a high tension was condensed in the tube leading from the ether bottle to the rectum and also in the rectum itself, and was both a source of irritation and the probable cause of the diarrhœa and melena. These objections were done away with by the introduction of Cunningham's method. He placed the ether flask in a water-bath at 37° C., just below the boiling-point of ether; this prevented any condensation of the ether vapor, absorption taking place so rapidly that it was impossible to have any fluid ether in the rectum. With this idea in view several forms of apparatus have been constructed (Leggett, *Annals of Surgery*, October, 1907; Viron, *Presse Médicale*, 1906). They are all on the same principle. A graduated flask is filled two-thirds with ether and corked. Through the rubber cork two glass tubes are inserted, the one, connected with the afferent tube, through which air is pumped by a Davidson's syringe, going to the bottom of the flask; the other, connected with the efferent tube leading to the rectum, is flush with the under surface of the cork, i.e., it does not dip into the ether. The ether flask itself is placed in a water-bath at 37° C. (98.6° F.). Between the efferent tube from the ether flask and the rectal tube a Y-shaped piece of glass tubing is inserted so that the rectum can be emptied of gas or ether at any time; or instead of this arrangement a double-current rectal tube is used, the ether vapor going into the rectum through one side while the excess vapor is led out of the rectum by the other through a rubber tube dipped 3 cm. in a flask containing alcohol, thus doing away with any stopcock arrangement as is necessary when the Y-shaped tube is used.

No matter what apparatus is used, the ether must not boil. The bowels must be thoroughly emptied; if this is not done anæsthesia will be impossible because the fæces prevent absorption or plug up the rectal tube, which must be inserted about ten inches. Colicky pains also may be caused after the anæsthesia if the bowels are not thoroughly empty beforehand. When the anæsthetic is first introduced the patient experiences a sensation of fullness and a desire to defecate, which is overcome by allowing passage of the vapor through the exhaust tube. At first the bulb is squeezed every

five or ten seconds; after fifteen minutes, when the patient is under the influence of the anæsthetic, two or three times a minute is enough. Care should be taken not to allow the jaw to fall back, as this interferes with respiration. If the patient seems to get too much ether, pressure on the abdomen will always force out any excess of ether vapor.

Advantages.—Small quantities are used, none is wasted, there is no choking sensation or struggling as the patient goes under, little or no vomiting occurs afterward, quick recovery follows, and there is less bronchial secretion and salivation. It causes no vomiting even when anæsthesia is induced after a hearty breakfast. It facilitates the performance of operations about the head, mouth, and neck as well as insures better asepsis. It is supposed to be less dangerous, as the lungs are free to eliminate the ether, as it is absorbed, acting as a sort of a safety valve. It is to be preferred in any kind of lung disease, for even though it is eliminated by the lungs, the direct irritation of the concentrated ether is overcome. Patients who have been anæsthetized by rectum and by mouth prefer the former.

Disadvantages.—It takes longer to get the patient under. The method cannot be used where there is any abdominal distention or rectal disease. It sometimes causes a distention of the intestine which hampers the operator during a laparotomy. Even though there have been practically no cases of diarrhœa and melena since Cunningham's method was used, the cases reported are too few to exclude positively these complications from the list of disadvantages.

Conclusions.—In the cases in which ether has been given by the rectum according to Cunningham's method there have been no deaths and almost no cases of diarrhœa and bloody stools. If further trials give similar good results this form of anæsthesia would seem to be advisable in certain cases, but on account of the limited experience its employment is at present warranted only in exceptional cases. Its range of adaptability can be measured only by a more extended experience.

C. Frederic Jellinghaus.

ANÆSTHESIA, SCOPOLAMINE - MORPHINE.—In 1891 Ernst Schmidt discovered an alkaloid which existed in the root of various species of the genus *Scopolia*, a plant named after Scopol, an Austrian naturalist; this alkaloid he called scopolamine hydrobromate. In reviewing pharmaceutical literature one is struck by the varied reports as to the relation of this drug to hyoscine hydrobromate, an alkaloid of hyoscyamus; some claim they are identical, others hold that they are not. Hyoscyamus was used as an anæsthetic in the Middle Ages, and to-day hyoscine is used as an anæsthetic by some in the same manner as scopolamine though much less frequently. In 1900 Schneiderlin advocated the hypodermic use of scopolamine with morphine as a substitute for a general anæsthetic and soon after Steinbüchel introduced the combination into obstetrics. The uses of the mixture are three in number: (1) as a general anæsthetic; (2) as an aid to chloroform and ether narcosis; (3) as a partial anæsthetic in obstetrics.

Action.—Without going into any details as regards the physiological action, we may say that soon after its administration the patient becomes drowsy, the face slightly red, the throat dry, the pupils dilated, and if the dose was large enough he finally goes to sleep (becomes anæsthetized). This action, however, is not uniform and the drug may cause a variety of bad effects, no matter how small the dose; instead of becoming drowsy the patient may not be affected at all, or he may become excited and insist upon walking around, and the redness of face, thirst, and dry mouth may become extreme. There may be difficulty in swallowing, slowed, irregular, stertorous breathing, melano-pia, hyperacuis, dizziness, hyperemesis, delirium, hallucinations, and death from cardiac or respiratory failure.

General Anæsthetic.—A large quantity may be given in divided doses over a period from one to three hours before operation, or a single large dose may be given. In the latter case 0.0008 gram scopolamine with 0.02 gram of morphine is given one hour before operation, and if fifteen minutes before the scheduled time the narcosis is not deep enough an additional dose of 0.0002 gram scopolamine and 0.005 gram morphine is given hypodermatically. If given in divided doses a solution of scopolamine 0.001, morphine 0.025, water 10.0 is divided into three parts and a dose given two and one-half, one and one-half, and one-half hour before operation.

The mixture is supposed to cause general anæsthesia, but its efficacy in this respect is denied by some. Thus Dirk found in 260 cases only 29 which required no other anæsthesia; Israel reports 332 cases, of which only 32 required no other anæsthesia; of Zaratnicky's 232 cases only 100 required no other anæsthesia, and Stolz, in 465 cases had only 156 which required no other anæsthesia. Blois reported 100 cases with a mortality of one per cent., much higher than that of chloroform or ether. This high mortality, the liability to disagreeable or dangerous after-effects or complications, and the uncertainty in anæsthetic effects render the employment of this method inadvisable in the production of general anæsthesia.

As an Aid to Other Anæsthetics.—To accomplish this 0.0005 scopolamine and 0.01 morphine are given one-half to one hour before operation. When this is done the patients take the ether or chloroform more quietly, there is rarely any vomiting during anæsthesia (this is also true when chloroform or ether is used alone); they come out of the anæsthetic without excitement; post-operative vomiting is absent or rare, there is less salivation, less liability to bronchitis and pneumonia. Only half as much chloroform or ether is used as ordinarily. Seelig and others have reported good results with this method, but others have noted bad after-effects, including death. Furthermore, scopolamine usually causes a dilatation of the pupil so that the latter can no longer be used as a guide in the subsequent employment of chloroform or ether.

In Obstetrics.—Here the method finds its most extensive use. The questions that arise are: when should it be given and how deep a narcosis should be produced? Most obstetricians agree that if it is given at all it should be given only in normal cases at a time when pains are good and regular (every five minutes) and when labor could be completed immediately without much danger to mother or child, i.e., when the cervix is thinned out and dilated so as to admit at least three fingers. Some obstetricians desire only to produce sleep between contractions, when the latter will still cause some pain, while others give enough of the mixture to cause amnesia, during which contractions continue but are practically painless. The usual initial dose is 0.00045 gram scopolamine with 0.01 morphine; further doses of 0.00015 scopolamine without morphine being given at intervals of one to two hours until the desired effect is obtained. During this time the foetal heart must be carefully watched, the drug being contra-indicated if the pains are poor or the patient has fever.

The object of the drug is to make labor painless or almost so; some even claim that it shortens labor. An average of numerous published statistics shows the following:

Effect on contractions	1. Remain strong	60
	2. Weaker or less frequent	33
	3. Stopped	7
Effect on actual pain	1. Pain absent	52
	2. Pain lessened	30
	3. No effect on pain	18
Effect on contractions of recti	1. Good contractions remained	74
	2. Contractions slightly less	10
	3. Contractions much less	10
	4. Contractions absent	6

Perfect results with no bad after-effects are obtained only in 25 to 35 per cent. of the cases. Objections which have been brought against the method are that labor is frequently actually prolonged, that instrumental delivery is necessary in 10 to 16 per cent. of the cases, often because of the poor foetal heart. Eighteen per cent. of the children are apnoeic at birth, 3 to 5 per cent. are stillborn. The use of the drug predisposes to post-partum hemorrhage and subinvolution. Tears are more frequent because the patient uses her recti to the end, being too drowsy to respond to any request not to bear down. Viron and Morel collected 2,000 cases with 25 deaths; Roith, 4,000 with 18 deaths, 11 of which received only $\frac{1}{4}$ to 1 mg. of scopolamine. In spite of the results being perfect in some cases, the above reasons (the possibility of bad after-effects, and the mortality) all speak against the general use of the drug. Furthermore, even the advocates of the mixture admit that both mother and foetus require careful and constant attention, which makes its use in obstetrics impracticable.

C. Frederic Jellinghaus.

ANÆSTHESIA, SPINAL.—Since the publication of the article on "Spinal Cocainization and Lumbar Puncture," in volume vii. of this work, experiments with various substances for the production of medullary anæsthesia and the accumulated experience in all parts of the world have added materially to the fund of knowledge relating to this subject.

In the early history of spinal anæsthesia, only cocaine was used, but more recently other drugs representative of the sensory nerve depressant class have been tried with greater or less success. Among these are tropacocaine, eucaine, stovaine, novocaine, alypin, nirvanin, etc. Cocaine and some of the other drugs enumerated have also been used in combination with suprarenal extract, and alone preceded by the hypodermic administration of scopolamine and morphine. Still more recently, magnesium sulphate has been advanced as a spinal analgesic, and special claims have been made in its behalf on account of its very pronounced inhibitory powers.

Of all the drugs adapted to subarachnoid injection, tropacocaine seems to be, at present, the most satisfactory and the least harmful. It resembles in action cocaine, but it is much less toxic, while in the same dose it is equally efficient. Suprarenal extract in combination with tropacocaine is approved and constantly used by some operators; but it is condemned and rejected by others, and is regarded by some of them as worse than useless. The preliminary hypodermic use of scopolamine, grain $\frac{1}{100}$, and morphine, grain $\frac{1}{4}$, has become a routine practice with many prominent surgeons, who attach much importance to this simple supplementary measure.

Eucaine, like other preparations of this group, is a synthetic compound allied chemically to cocaine. Eucaine, or rather beta-eucaine, is thought to possess some advantages over cocaine as a spinal anæsthetic. It is somewhat less toxic, the solutions are more stable, and boiling does not impair its properties. On the other hand, the resultant anæsthesia is said to be not so uniform or so lasting. Stovaine, novocaine, alypin, and nirvanin are similar in effect and are closely allied both chemically and therapeutically to cocaine. It is not admitted that these preparations are superior in any respect to tropacocaine or to beta-eucaine.

The interesting experiments of Dr. S. J. Meltzer, of the Rockefeller Institute for Medical Research, demonstrating the remarkable effect of the magnesium salts when injected into the spinal canal, have attracted general and profound interest. It has been conclusively shown that common Epsom salt, when so used, is capable of inducing complete insensibility to pain, and the original experiments upon monkeys have been verified and confirmed by actual tests upon human subjects.

The technique is identical with that employed in lumbar puncture. An amount of spinal fluid is with-

drawn equal in bulk to the solution to be injected. A twenty-five-per-cent. thoroughly sterile aqueous solution of a chemically pure salt is used. The dose usually recommended is about one-third to one-half grain for every two pounds of body weight. Limited anæsthesia ensues in about forty-five minutes, and deep general anæsthesia, with paralysis of the legs and abolition of the tendon reflexes, follows after three or four hours. This state may continue for several hours and, although analgesia may be complete, the tactile sense sometimes remains and the vital reflexes are not appreciably affected. Under its influence abdominal and pelvic operations and various operations upon the lower extremities have been successfully performed; it is, moreover, stated that with a sufficient dose operations upon any part of the body may be rendered painless. So far the results of the subdural injection of the magnesium salts have not been uniform, but, on the contrary, have proved extremely variable and uncertain.

The after-effects in some cases have been severe, protracted, and really alarming. Among these are headache, fever, nausea, vomiting, mental confusion, incoherence, coma, paresis, incontinence of feces, retention of urine, and retarded respiration. It is claimed that the graver symptoms may be modified and their duration abridged by again puncturing the membranes, after the operation is concluded, withdrawing a small quantity of the spinal fluid and then irrigating the canal by injecting, several times in succession, normal salt solution, finally leaving a small portion of the solution in the canal.

It has been found that severe tetanic convulsions with opisthotonos, artificially produced in monkeys by the tetanus toxin, may be entirely relieved for many hours by the intraspinal injection of magnesium sulphate, and, in view of the uniform effect upon the voluntary muscles—the prolonged paralysis—which follows the injection of the salt, this treatment was suggested as available and has been employed in tetanus. Following this suggestion, several cases of tetanus have been reported in which repeated injections were used with apparently good results and followed by ultimate recovery, even after the seeming failure of the antitetanic serum. A number of cases have also been recorded in which the injection of the magnesium salt was fairly tried without permanent benefit. At best, this treatment can be regarded as only symptomatic and its application is probably very limited. Prior to the use of magnesium sulphate, however, spinal anæsthesia by means of beta-eucaine and morphine had been successfully employed in the treatment of tetanus.

The whole question of spinal anæsthesia, notwithstanding the confident assertions of some enthusiasts, must be considered as yet in the experimental stage, and the practice cannot, therefore, be recommended for general use or indorsed as a trustworthy surgical resource. It is by no means so innocent a measure as its more ardent advocates sometimes assume, and the undeniable fact remains that, no matter what preparation is used, the procedure as now practised is attended with considerable immediate and, possibly, with no little remote danger.

James B. Baird.

ANAPHYLAXIS (*ἀνα*, against, and *φύλαξ*, guard, or *φύλαξις*, protection), also called hypersusceptibility, supersensitiveness, is a condition of unusual or exaggerated susceptibility of the organism to foreign proteids. The word anaphylaxis suggests the contrary condition to prophylaxis; it may be congenital or acquired; it is specific in nature. The condition of Anaphylaxis may be brought about by the introduction of any strange proteid into the body. Hypersusceptibility to proteids that are non-poisonous in themselves may readily be induced in certain animals.

An animal may be in a condition of hypersusceptibility and immunity at the same time. The two conditions are closely interwoven. The one may be dependent upon the other. Pirquet advises that the

term *Immunity* be limited to indicate the condition of complete resistance in which no clinical reaction occurs, when poisons (such as diphtheria, tetanus, etc.), are introduced into the organism. He suggests the term "*Allergie*" to indicate those conditions of acquired immunity associated with anaphylaxis, such as that induced by vaccinia against variola, that of the luetic against syphilis, of that produced by one attack of some of the acute specific infections. This condition of *allergie* manifests itself in the renewal of the infection in an entirely different manner from the reaction to the primary infection.

The tuberculin and mallein reactions are well-known instances of anaphylaxis. These substances are not poisonous when introduced into a healthy individual, but the tuberculous individual is anaphylactic to tuberculin, and an individual suffering with glanders is in a state of hypersusceptibility to mallein.

The best studied instance of anaphylaxis is that produced in the guinea-pig by the injection of a foreign protein, for example, horse serum, egg white, milk, etc. Especial study has been made of the anaphylactic action of the blood serum of the horse, because that serum is so much used in serumtherapy.

It has long been known that the blood of certain animals is poisonous when transfused or injected into certain other species. Many instances might be cited showing that the blood serum of one animal has poisonous properties when injected into an animal of another species. But the blood serum of the horse apparently lacks such poisonous action. Very large quantities of the blood serum of the horse may be injected into man, rabbits, guinea-pigs, and many other animals without serious inconvenience, except occasionally a slight reaction at the site of inoculation.

In a certain proportion of cases the injection of horse serum into man is followed by urticarial eruptions, joint pains, fever, swelling of the lymph nodes, cedema, and albuminuria. This reaction, which appears after an incubation period of eight to thirteen days, has been termed by Pirquet and Schick the "serum disease." In exceptional instances sudden death has followed an injection of horse serum in man.

Our studies were taken up in October, 1905, in order to throw light upon the cause of this unfortunate accident. We have shown that ordinarily horse serum is a comparatively bland and harmless substance when injected into certain animals; but these animals may be rendered so susceptible that an injection of horse serum may produce sudden death or severe symptoms. For example, large quantities of horse serum may be injected subcutaneously or into the peritoneal cavity of a guinea-pig without apparently causing the animal the least inconvenience. However, if a guinea-pig is injected with a small quantity, say $\frac{1}{25}$ c.c., of horse serum, and after the expiration of a certain interval is again injected with horse serum, the result will probably be fatal. The first injection of horse serum has sensitized the animal in such a way as to render it very susceptible to a toxic principle in horse serum.

A certain time is necessary to elapse between the first and second injections of horse serum before this toxic action is able to manifest itself. This "period of incubation" is from ten to twelve days, and corresponds suggestively with the period of incubation of the serum disease which Pirquet and Schick place at eight to thirteen days. Guinea-pigs may be sensitized with exceedingly small quantities of horse serum. In most of our work we used quantities less than $\frac{1}{25}$ c.c. and we found in one instance that $\frac{1}{1000}$ c.c. of horse serum was sufficient to render a guinea-pig susceptible.

It also requires very small quantities of horse serum, when given in a second injection, to produce poisonous symptoms. One-tenth c.c. injected into the peritoneal cavity is sufficient to cause the death of a half-grown guinea-pig. One-tenth c.c. of horse serum injected subcutaneously is sufficient to produce serious symptoms. The fact that this toxic action may be de-

veloped by such small quantities of serum, and the fact that exceedingly small quantities are sufficient to sensitize the animal, *a priori*, place both the sensitizing and the toxic principle in the horse serum in the "haptin group" of substances in the sense used by Ehrlich.

A still further indication that the side-chain theory in its broadest sense may be applicable is the further fact that immunity may be produced against the toxic action by multiple injections of the serum.

While at first we thought that diphtheria antitoxin had some relation to this action, we are now able to state positively that it has nothing whatever to do with the poisonous action of horse serum; further, that diphtheria antitoxin in itself is absolutely harmless. The toxic action which we have studied is caused by a principle in normal horse serum and is entirely independent of the antitoxic properties of the serum.

Historical.—The fact that guinea-pigs which had been used for the testing of diphtheria antitoxin frequently died when later given an injection of serum has been known almost since the discovery of diphtheria antitoxin, but no one seems to have noticed any connection between the two injections until 1905. Most of the workers with serum regarded it as an accident pure and simple or that the animal's vital resistance had been lowered by the first treatment; some even thought that it was the effect of cold, as the serums were usually kept in the ice chest and were injected at once after removing from the ice box. Theobald Smith, however, evidently had the problem in mind, as he spoke to Ehrlich about it when the latter was in this country in 1904, and the result was Otto's work. When we first encountered the phenomenon it at once occurred to us that there might be some relation between it and sudden death after the injection of antitoxin in man and our work was begun in the hope of throwing light on this unfortunate accident. The results of our work on this most interesting subject have been published in a number of papers¹ since April, 1906. We foresaw early that the phenomenon very probably had a close relation to immunity, and our recent work with proteids obtained from the bacterial cells have shown this to be true. We have been able to produce anaphylaxis in guinea-pigs with bacterial extracts and have found that these animals possessed an immunity to the corresponding infections.

Early in the last century (1839) Magendie² found that rabbits which had tolerated two intravenous injections of egg albumin without any ill effects immediately succumbed to a further injection made after a number of days. Later, workers with precipitins frequently found that some of their animals died suddenly during the course of treatment from no apparent cause, while what really happened was they were in a state of anaphylaxis to the foreign proteid. Other analogous instances may be found scattered throughout the literature.

Knorr³ (1895) found that guinea-pigs develop an increasing sensitiveness to tetanus toxin.

Hericourt and Richet⁴ (1898), in studying the effects of eel serum on dogs, found that they were not able to immunize them against the serum, but that on the contrary there was an increasing sensibility to the serum, so that finally the dogs died.

Behring and Kitashima⁵ (1901), repeating some of Knorr's work, also found an increasing sensitiveness to tetanus toxin on the part of guinea-pigs.

Portier and Richet⁶ (1902) found that if dogs were given a very small dose of a glycerin extract from the tentacles of actinia, and then in fifteen or twenty days given a second small dose, the animals quickly succumbed. The dose given was so small as to cause no symptoms in a normal animal. They appear to be the first to use the word "anaphylaxis" to indicate hypersensitiveness to a poison.

Arthus⁷ (1903) studied the effect of repeated injections of horse serum on rabbits and found that if the rabbit be given repeated injections of horse serum at

some days' interval it caused, even in small doses, results which, according to the number of the previous injections and methods of injection, were local or general, benign or grave.

Riche⁸ (1904-05), in studying two poisons (congestin and thalassin) extracted from actinia, found that if a very small dose of them, which caused practically no symptoms in a dog, was followed after twenty-two days by another small dose, the animal became very sick or quickly died.

Pirquet and Schick⁹ in 1905, in a monograph upon the "serum disease," described in detail this syndrome which sometimes follows injections of horse serum in man. They show that the symptoms of this "disease," when caused by a second injection, may either appear at once (the "immediate" reaction) or after a shortened period of incubation (the "accelerated reaction").

Pirquet and Schick draw original and far-reaching conclusions showing the relation of these clinical observations to hypersusceptibility, and the importance of these facts in general pathology. They draw attention to the analogy to the tuberculin reaction as a well-known instance of hypersusceptibility. Pirquet and Schick believe that the serum reactions give a possible explanation of the period of incubation of infectious diseases, and finally conclude that the immunity caused by vaccinia and a group of infections is due to the power of "immediate" reaction acquired by the organism.

During Ehrlich's visit to this country in 1904 Theobald Smith told him that guinea-pigs which had been used in testing the potency of diphtheria antitoxin become acutely sick or die if injected subcutaneously several weeks later with several cubic centimetres of normal horse serum. Ehrlich gave the problem to Otto, who worked out many of the essential features of the phenomenon. This article, published late in 1905,¹⁰ came to our attention while we were correcting the page proofs of our first article upon the same subject. It seems that the work was done about the same time, but Otto's paper appeared first. Otto showed what is now well known to be the result of a second injection of horse serum into guinea-pigs. He demonstrated that the diphtheria poisons play no part in the phenomenon. However, he found that guinea-pigs first treated with mixtures of diphtheria toxin and serum are more susceptible than those treated with serum alone. Otto showed further that immunity to the poisonous action of the serum may be acquired by repeated injections of large amounts of serum at short intervals. He demonstrated that this hypersusceptibility bears no relation to the specific precipitins. Finally Otto discusses the relation of the Theobald Smith phenomenon to the cases of reinjection in man, and cites instances of alarming symptoms following the second injection of antitoxic horse serum.

Many phases of the subject were studied by Rosenau and Anderson¹¹ late in 1905 and early in 1906. They studied particularly serum-anaphylaxis in the guinea-pig. They showed that a single injection of horse serum was harmless to a normal guinea-pig, but that a second injection after a definite interval was usually fatal. This "period of incubation" was found to be about ten days. The poisonous property was shown to have absolutely no connection with the antitoxic property of the serum or with the diphtheria toxins.

The poisonous principle in serum was found to be quantitatively specific; death occurring at the second injection with the homologous serum only and never with the heterologous. Hemolysis and precipitin formation were excluded as factors. The poisonous property was unaffected by various chemical, physical, and mechanical influences and by age. Guinea-pigs may be sensitized with 1.000.000 c.c. of serum and then remain sensitive for a very long time. They were able to sensitize guinea-pigs by feeding them horse meat or horse serum. They showed further that the offspring of sensitive female guinea-pigs were sensitive to a first

injection of serum; this being the first instance of the experimental demonstration of the hereditary transmission of a hypersusceptibility to a disease.

Anderson¹² found that female guinea-pigs could transmit to the same offspring hypersusceptibility to horse serum and immunity to diphtheria toxin. This fact is of great importance in testing antitoxic sera and necessitates care in the selection of breeders for guinea-pigs to be used in serum work.

McClintock and King¹³ (1906) gave ten guinea-pigs from $\frac{1}{8}$ to 1 c.c. of horse serum by the stomach, and thirteen days later 6 c.c. of serum, either subcutaneously or intraperitoneally, without causing symptoms in any of them. They conclude that the sensitizing action of horse serum given by the mouth is not nearly so great as when given subcutaneously or intraperitoneally. This is in confirmation of our reported experiments.

Currie¹⁴ (1907) has studied the effect of repeated injections of horse serum in persons admitted for treatment in the city of Glasgow Fever and Smallpox Hospital at Belvidere. He concludes that it is apparent from the facts detailed by him that repeated injections of horse serum induce symptoms of supersensitization in man, but it is also apparent that the same facts lend no countenance to the suggestion that the death of persons suffering from diphtheria is to be apprehended as the result of repeated injections of antidiphtheric serum.

Besredka and Steinhardt¹⁵ (1907) studied with much care certain features of hypersusceptibility to horse serum in guinea-pigs; they note that the French serums are much less toxic than those used by Otto in Frankfurt and the serums used by us. Besredka and Steinhardt had a mortality of about 25 per cent., when 5 c.c. of serum was given intraperitoneally at the second injection, whereas death was the rule in our experiments under similar conditions. Most of their work was done with doses of 0.05 to 0.25 c.c. given directly into the brain, which either killed or caused grave symptoms in susceptible guinea-pigs. Besredka and Steinhardt lay stress upon the production of "anti-anaphylaxis," which we termed "immunity." They found that a single injection of serum given into the peritoneum of a sensitized guinea-pig conferred immunity to a subsequent injection of 0.25 c.c. into the brain; in one case the anti-anaphylaxis was present one and a half hours after the injection into the abdominal cavity. They were unable to demonstrate any protective properties in various organs of immune guinea-pigs, confirming our work along the same lines.

Nicoll¹⁶ (1907) found that guinea-pigs were not susceptible to the necrotic action induced by repeated injections of horse serum, as is the case in rabbits; this corresponds with our observations. He also found that daily injections or "spaced" injections, after the method of Arthus, did not induce a high degree of hypersusceptibility in guinea-pigs.

Besredka¹⁷ (1907) questions whether we should not consider this toxic property of horse serum, as well as its antitoxic power. He suggests that a serum, 0.05 c.c. of which when given into the brain will kill or cause grave symptoms in a sensitive guinea-pig, should be considered as above the average toxicity and ought to be excluded from use in man.

Rosenau and Anderson¹⁸ (1907) in a further contribution to the subject studied particularly the relation of anaphylaxis to immunity. In addition to confirming and extending their work on the specific nature of the phenomenon, they made observations on the relation of various physical influences and chemical substances on the reaction. They brought out the important fact that proteids extracted from the bacterial cells and injected into guinea-pigs produced on the second injection the same train of symptoms as in the case of serum-anaphylaxis. It was found that in certain instances the hypersusceptibility produced by those bacterial extracts left the animal immune to the corresponding infection.

Vaughan¹⁹ (1906) advanced the theory that the first injection of the strange proteid is broken up into components, one of which is toxic, but that the animal is not poisoned because this breaking up takes place slowly. The cells, however, learn from this lesson how to break up the complex molecule, so that when more of the strange proteid is introduced at the second injection it is violently rent asunder, quickly liberating large quantities of the toxic principle of the complex molecule.

Vaughan and Wheeler²⁰ (1907) have elaborated this explanation by further studies upon egg white and bacterial proteids split into poisonous and non-poisonous portions. These authors believe that when egg white, or the non-poisonous portion of egg white, is injected into a fresh animal certain cells of the body are so influenced that they elaborate a new ferment, which, in the form of zymogen, remains in the cell until activated by the second injection, when it is set free and splits up the egg white in a manner similar to that used by Vaughan in the laboratory. Vaughan and Wheeler believe that the effect induced in the animal is the same as that caused by the poisonous portions of egg white as they have split it up in the retort.

Gay and Southard²¹ (1907) found in guinea-pigs dying from a second injection of serum, and in those which had severe symptoms and were later chloroformed, what they considered characteristic lesions. Considerable hemorrhages, rather definitely localized, are the characteristic gross lesion. The hemorrhages may be in one or several organs; gastric hemorrhages being especially frequent. Microscopically, there are in addition to the naked-eye hemorrhages minute interstitial and oozing hemorrhages. They also claimed to have found fatty changes in voluntary-muscle fibres, heart-muscle fibres, and in nerve fibres.

Their explanation of serum anaphylaxis in the guinea-pig is as follows: There is a substance in horse serum (*anaphylactin*) which is not absorbed by the guinea-pig tissue, is not neutralized, and is eliminated with great slowness from the body. When a guinea-pig is injected with a small amount of horse serum the greater part of its elements are quickly got rid of; the anaphylactin remains and acts as a constant irritant to the body cells, so that their avidity for the other elements of horse serum is greatly increased. At the end of two weeks of constant stimulation by the anaphylactin a condition is arrived at where, if the cells are suddenly presented with a large amount of horse serum, they are overwhelmed in the exercise of their increased assimilating functions, and functional equilibrium is so disturbed that local or general death may occur.

Besredka and Steinhart²² (1907) found that guinea-pigs could be put in a state of anti-anaphylaxis by the injection of horse serum into the brain as well as into the peritoneal cavity. They consider it a phenomenon of the same order as the disintoxication *in vitro* of the tetanized brain by antitetanic serum. They found that guinea-pigs could not be sensitized by intracerebral injection.

They think that their results seem to indicate that the phenomena of anaphylaxis and anti-anaphylaxis are similar to the precipitating and absorbing actions which govern the relation of colloids among themselves.

Besredka²³ (1907) confirms our published work that the toxicity of horse serum is destroyed by heating to 100° C.; he also states that it is markedly attenuated by varying degrees of temperature down to 55° to 50° C. He found that injection of calcium chloride the day before prevented the appearance of anaphylactic symptoms.

In a second paper, Otto,²⁴ in 1907, showed that animals may be sensitized by injecting them with the serum of sensitized animals. He believes that the first injection results in a weakening or disappearance of the portion ("rests") of the antigens which are in the body, and thus an apparent "hypersusceptibility" results. The duration of this hypersusceptibility depends upon the amount of serum injected the first time.

Richet²⁵ (1907) gives a general review of the subject of anaphylaxis and also some very interesting work on anaphylaxis produced by a substance obtained from *Mytilus edulis*. He found that the blood of a dog sensitized by this substance when injected into an untreated dog sensitized the animal to an injection two days later of the extract.

He thinks that anaphylaxis is due to the presence of a toxicogenic substance, non-toxic of itself, but producing a poison by reaction with the second injection of the extract. In support of this view he states that *in vitro* a mixture of the serum of a sensitized dog and of the extract is more toxic than the extract alone.

Goodall²⁶ gives observations on ninety patients who had received two injections of horse serum; of these 43.4 gave either an immediate or accelerated reaction.

Besredka²⁷ (1907) concludes that the toxicity of therapeutic serums may be measured by means of intracerebral injections into sensitized guinea-pigs. Measured in this way, different serums show a wide gamut of toxicity, the fatal dose varying from $\frac{1}{4}$ to $\frac{1}{16}$ c.c. This toxicity resides in the serum and not in the cellular elements. The serum of horses living under apparently the same conditions have about the same toxicity; individual variations are rare and of little importance. The difference in the toxicity of serums appears to be due, in the first place, to their origin, and, in the second place, to their age. Serums are hypertoxic on the day of bleeding, and gradually lose their toxicity. This loss, rapid at first, becomes gradual after the tenth day. All therapeutic serums should be considered toxic within two months of bleeding. In a general way, all serums that excite grave anaphylactic phenomena in doses of $\frac{1}{16}$ to $\frac{1}{32}$ c.c., and, *a fortiori*, above this amount, should be considered toxic. Besredka finally states that the technique of dosage by the intracerebral method is rapid, simple, and not expensive.

Serum Anaphylaxis.—Horse serum, either normal or antitoxic, when injected into normal guinea-pigs, causes no symptoms. By "normal" guinea-pigs is meant animals that have not previously received treatment of any kind and were born of untreated mothers.

As much as 20 c.c. may be injected into the peritoneal cavity of a guinea-pig without causing any apparent inconvenience to the animal. When injected subcutaneously there may be a slight local reaction, which disappears in a few hours. Small amounts of horse serum, such as 0.25 c.c., may be injected directly into the brain without causing any untoward symptoms. If, however, horse serum be injected into a used guinea-pig the result is almost invariably fatal. By a "used" or "treated" guinea-pig we mean one that has recovered from the effects of an inoculation of the toxin-antitoxin mixture used in testing the potency of antitoxic serum, or one that has received a prior injection of horse serum.

Very characteristic symptoms are produced by horse serum, either normal or antitoxic, when injected into a susceptible guinea-pig. The symptoms are apparently the same whether the injection is made subcutaneously or into the peritoneal cavity, or whether normal or antitoxic horse serum is used. In five or ten minutes after injection the pig manifests indications of respiratory embarrassment by scratching at the mouth, coughing, and sometimes by spasmodic, rapid, or irregular breathing; the pig becomes restless and agitated. This stage of exhalation is soon followed by one of paresis or complete paralysis. The pig is unable to stand or, if it attempts to move, falls upon its side; when taken up it is limp. Spasmodic, jerky, and convulsive movements now supervene.

Pigs in this stage with complete paralysis may fully recover, but usually convulsions appear, and are almost invariably a forerunner of death. Symptoms appear about ten minutes after the injection has been given; occasionally in pigs not very susceptible they are delayed thirty to forty-five minutes. Only in one or two instances of the several hundred pigs which we have

observed have the symptoms developed after one hour. Pigs developing symptoms as late as this are not very susceptible and do not die. The chain of symptoms is exceedingly characteristic. The symptoms do not always follow in the order given. Death usually occurs within an hour and frequently in less than thirty minutes.

If the second injection be made directly into the brain the symptoms are manifested with explosive violence, the animal frequently dying within two to three minutes. The same is also true if the second injection be made directly into the heart.

Judging from the symptoms produced by the injection of horse serum into a susceptible guinea-pig we assumed that the poison acted upon the nervous system. Autopsies done immediately after the death of the guinea-pigs showed invariably that the heart continued to beat long after respiration had ceased. In some instances the heart would continue to beat a full hour when exposed. This would seem to indicate that we were dealing with a poison which caused death through the nervous control of the respiration.

A sensitive guinea-pig was given an injection of serum causing the death of the animal in thirty minutes. Immediately after death the phrenic nerve was exposed and stimulated high up, causing contractions of the diaphragm both upon making and breaking the galvanic current. The contractions were also caused with the induced current. The contractions of the diaphragm caused by stimulating the phrenic nerve in this way were produced with a weaker current than those required to cause similar contractions in a normal control guinea-pig.

By a series of experiments we were able definitely to establish the fact that this toxic property of serum had no relation to infections with the *B. diphtheriae*, or to injections of the toxin and toxon, and bore absolutely no relation to the antitoxic content of the serum. Normal horse serum is as poisonous to a sensitive animal as antitoxic horse serum. An animal may be sensitized as readily with normal serum and subsequently poisoned with normal serum as with antitoxic serum. This property is inherent in blood serum and bears no relation to its antitoxic properties.

We are of the opinion that the substance which sensitizes the guinea-pig is perhaps the same as that which later poisons it. Profound chemical changes, perhaps in the central nerve cells, are probably produced by the first injection. We devoted much time to the isolation of this sensitizing principle, without success.

It is unaffected by the various preservatives used for the preservation of antitoxic serum; by drying; by precipitation with ammonium sulphate or magnesium sulphate; and by the admixture with diphtheria or tetanus toxins. Formaldehyde likewise has no influence upon this principle. Serum heated to 60° C. for thirty minutes is as potent in sensitizing animals to a subsequent injection as the unheated serum.

The removal of the spleen or the thyroid from the animal before or after receiving the sensitizing dose, apparently has no influence upon the development of anaphylaxis.

Gay and Southard²¹ first pointed out that if the blood of a guinea-pig which has received a small sensitizing dose of normal horse serum be drawn, the serum collected, and 1.5 c.c. of this be given to a normal guinea-pig, the normal animal is rendered susceptible to a subsequent injection of horse serum given fifteen days later. This shows that the sensitizing substance, or *anaphylactin*, as it is called, is present in the blood serum of a sensitive animal. It must be present in an exceedingly minute amount, as we have shown that the blood of guinea-pigs receiving only 0.05 c.c. of serum contains this substance many months later, and that 1.5 c.c. when injected into a normal animal renders it sensitive to a subsequent injection of horse serum.

Guinea-pigs may be sensitized by either large or small amounts of serum. Amounts as great as 10 c.c. have sensitized the animals, while amounts as minute

as 1/100,000 c.c. did likewise. The optimum sensitizing amount, however, appears to be from 1/100 to 1/1000 c.c.

It has appeared to us in our work that the animals are rendered slightly more sensitive if given a mixture of toxin-antitoxin used in testing serum. This may be due to the fact that the toxin, which is not completely neutralized by the serum or which becomes disassociated, may lower the resistance of the animal to some extent. Guinea-pigs are sensitized if the injection be given subcutaneously, intraperitoneally, directly into the heart, into the brain, or by the mouth.

The Toxic Principle.—At one time we made efforts to isolate the active principle in horse serum which causes the symptoms, but as soon as we realized that this principle present in horse serum exerts its action in quantities so minute as to place it almost in the category of the ferments, and, further, when we concluded from our work that this toxic principle is doubtless one of those highly organized and complex proteid substances belonging to the "haptin" group, we recognized how hopeless it would be with present technique to isolate this substance. Nevertheless, we devoted much time and study to its relation to various chemical, physical, and electrical influences. The practical importance of eliminating or neutralizing this toxic principle from horse serum is at once evident.

We heated serum for various lengths of time to 60°, 70°, 80°, 90°, and 100° C., and found that the toxic property is entirely destroyed by heating to 100° C. for twenty-five minutes. The toxic principle is not affected by various chemicals such as calcium chloride, sodium nitrate, magnesium sulphate, ammonium sulphate, and formaldehyd. It is not affected by various ferments, alkaloids, and similar substances, such as taka-dias-tase, pancreatin, rennin, myrosin, invertin, emulsin, pepsin in acid solution and in alkaline solution, ingluvin, malt, papain, atropine, strychnine, morphine, and caffeine. It is not affected by freezing at 15° F., or by filtration through porcelain, drying, precipitation, and dialysis, or exposure to the x-rays.

We found it interesting to compare the toxic effects upon sensitive animals of untreated antitoxic serum, and the precipitated and refined antitoxin; bulk for bulk we found them equally toxic. But as the same number of units can be given in half the bulk there is a manifest advantage in using the precipitated serum, as the rashes and untoward effects of serum depend to some extent upon the volume of serum administered.

The smallest amount of serum given intraperitoneally that we have found to cause death is 0.1 c.c. This amount, when given directly into the heart, is sufficient to cause the death of the animal, while 0.25 c.c. given into the brain is almost invariably fatal. In most of our work, however, we have used 5 or 6 c.c. of serum intraperitoneally, and this seems to be the favorite dose of other workers. Certain symptoms in guinea-pigs caused by a second injection of the serum suggested to us that the action might be due to hemolysis or the formation of precipitins. By a large number of experiments, however, we were able to exclude both hemolysis and the formation of precipitins as factors. The toxic action bears no relation, therefore, to hemolysis or to precipitin formation.

Early in our work the question arose whether the toxic action of horse serum was specific. We found it to be, for the various sera, quantitatively specific. That is, if a guinea-pig were sensitized with horse serum and then injected with hog serum, slight, if any, symptoms would result. The converse of this is also true. We tested some eight or ten different sera and found that death never occurred except when a homologous serum was given at the second injection. If, however, proteid substances of a widely different nature are used, the action then is absolutely specific. For example: If a guinea-pig is sensitized with horse serum and then subsequently injected with egg white or milk no results follow; but if the animal is sensitized at the first injection with egg white and then given a second injection

tion of egg white, the result is serious symptoms or death.

We have recently shown²³ that guinea-pigs may be in a state of anaphylaxis to three proteid substances at the same time, and respond to a subsequent injection of each of those substances. Thus guinea-pigs may be sensitized to horse serum, egg white, and milk. They may be sensitized at the same time by giving the injections of the substances in different parts of the body or by mixing the three and giving at one dose, or they may be sensitized at different times by giving the substances at intervals of fourteen days. If these animals are then given, after an interval of fourteen days from the last injection, an injection of any one of these three substances, either death or severe symptoms result. If death does not occur, the animal will react when tested on the next day with the second substance. If the experiment is fortunate he recovers, and is finally tested on the third day for the third substance, which may result in death. The guinea-pigs carry the three charges of the three proteids at the same time. They are in a condition of anaphylaxis to the three foreign proteid substances. Finally, they react to each one separately like three separate diseases.

Animals may have severe symptoms and appear almost moribund, but recover; and the recovery is always complete in twenty-four hours.

The experiments above alluded to have strengthened our belief that the phenomenon of anaphylaxis is not dependent upon morphological changes, but upon chemical changes induced by the action of the two injections of foreign proteid.

A certain time is necessary to elapse between the first and second injections of the foreign proteid before the toxic action is manifest. This "period of incubation" is from ten to twelve days and corresponds suggestively with the period of incubation of the serum disease, which von Pirquet and Schick place at eight to thirteen days, and with the period of incubation of some of the infectious diseases.

If a guinea-pig be given an injection of serum and then be injected any time before the eighth day no ill results follow. In other words, the animal has not had time to enter a state of anaphylaxis to the foreign proteid. If, however, the injection be given after the eighth or tenth day the animal is then in a state of anaphylaxis or hypersusceptibility to the foreign proteid. The shortest interval between the two injections in which we have found death to occur is twelve days. The animal, however, remains susceptible a very long time. The longest period which we have observed is 732 days between the first and the second treatment. We have no doubt, however, that the animal remains susceptible during its entire life.

Immunity to Anaphylaxis.—Guinea-pigs may be actively "immunized" against this hypersusceptibility. This may be done in several ways. One way is to give repeated injections for the first ten days before the animal reaches the stage of anaphylaxis. Another is to give a large primary inoculation and sublethal doses frequently repeated. We were unable to show that the blood serum or juices of any organ of an immunized guinea-pig could confer immunity upon a sensitized guinea-pig to subsequent injections of serum. It would, therefore, appear that the "immune body," if any such exists against the toxic action of horse serum, is not free in the blood or body juices, as is the case, for instance, in diphtheria.

Feeding Experiments.—Guinea-pigs may be sensitized by feeding meat or serum. Uhlenhuth²⁴ found that when rabbits are fed with egg-albumin by means of a stomach tube, their blood after a while develops the power to precipitate egg-albumin.

Metalnikoff²⁵ reports that he attained immunization by feeding one animal with the blood of another. He fed horses' blood to white rats, and noted that after several weeks the serum of the rats developed decided agglutinative and hemolytic properties.

We found that guinea-pigs could be sensitized by feeding them for some days on horse meat or dried horse serum mixed in with their food. We did not use a stomach tube, as the possibilities of making slight wounds in the esophageal or gastric mucosa would vitiate the feeding experiments, as we knew from our previous work that very small quantities could readily sensitize the animal to a subsequent injection of serum.

If the guinea-pigs that had been fed with horse meat or horse serum were injected with horse serum after an interval of at least fourteen days, they reacted in a characteristic manner.

We also found that guinea-pigs could be sensitized to cattle serum by feeding them with beef. Cooking the meat entirely destroyed its sensitizing properties.

The fact that guinea-pigs may be rendered susceptible by the feeding of strange proteid matter opens an interesting question as to whether sensitized guinea-pigs may also be poisoned by feeding with the same serum. If man can be sensitized in a similar way by the eating of certain proteid substances it may throw light upon those interesting and obscure cases in which the eating of fish and other sea food, etc., by certain individuals habitually causes sudden and sometimes serious symptoms.

Hereditary Transmission.—In the course of our work we had the opportunity to test the susceptibility of the young of susceptible female guinea-pigs and we found that hypersusceptibility to the toxic action of horse serum is always transmitted from the mother guinea-pig to her young. This function is solely maternal; the male takes no part whatever in the transmission of these acquired properties. Whether this maternal transmission is hereditary or congenital cannot be definitely stated. We are able to exclude the milk as a factor in transmitting the hypersusceptibility to the toxic action of horse serum by a series of exchange experiments.

"Exchange" experiments consist in at once placing guinea-pigs born of a susceptible mother to nurse with an untreated female and, in exchange, the young of the untreated female are at the same time placed to nurse with the susceptible female. From these "exchange" experiments we learn that the hypersusceptibility is not transmitted to the young in the milk.

We also learn from our experiments that hypersusceptibility may be transmitted from mother to young whether the mother is sensitized before or after conception. The fact that this influence may take place after conception might be taken to indicate that the transmission is congenital and not hereditary.

These results upon the hereditary transmission of the susceptibility to the poisonous action of horse serum in guinea-pigs may throw light upon the well-known inherited tendency to tuberculosis in children born of a tuberculous parent. There are certain analogies between the action of tuberculosis and horse serum. Both produce a hypersensitiveness and also a certain degree of immunity. Now that we have proved that this hypersensitiveness, or anaphylactic action, in the case of horse serum may be transmitted hereditarily in guinea-pigs, may it not throw light upon the fact that tuberculosis "runs in families"? While there are several recorded instances demonstrating that immunity to certain infectious diseases may be transmitted from a mother to her young, this is, as far as we know, the first recorded instance in which hypersensitiveness, or a tendency to a disease, has been experimentally shown to be hereditarily transmitted from a mother to her young.

Action of Horse Serum upon Man and Other Animals.—It may be that man cannot be sensitized in the same way that we have shown is the case with guinea-pigs. We made no human experiments, but have collected data obtained by others which have a direct bearing on this question. Pirquet and Schick injected children with antitoxic horse serum at intervals. It has been customary to immunize numbers of children, when exposed to diphtheria, with antitoxic horse serum at in-

tervals of from three to four weeks. We have no doubt that there are many such instances on record and, so far as we know, this practice has never caused death. Repeated injections of horse serum into man is not an infrequent occurrence. Patients suffering with diphtheria are often given injections of antitoxic serum at short and frequent intervals. It is also not rare for persons to have several attacks of diphtheria at long intervals and to be treated each time with antidiphtheritic serum. Certain serums—for example, the anti-tubercle serum of Maragliano, or the antirheumatic serum of Menzer—are habitually used by giving injections at intervals of days or weeks. In all of these cases of frequent and repeated injections the amount which has been injected and the interval between the injections must be taken into account in relation to this work. Pirquet and Schick in their work on "Serum-disease" give the following instances in which children received two injections of horse serum at intervals of from sixteen to forty-two days between the first and second injections.

Leopold H.—October 3d, 1902. 100 c.c. scarlet-fever serum (Moser). Eight days following this injection symptoms of the serum disease appeared and lasted several weeks. December 2d, 1902. Fifty days after the first injection patient received 2d c.c. antidiphtheritic serum under skin of arm. In fifteen minutes following this second injection stormy symptoms set in. The boy began to cry and complained of nausea. (Edema of the lip set in and soon spread over the whole face. In several hours general urticaria.

Heinrich K.—Three years old. June 13th, 1902. 100 c.c. scarlet-fever serum. On the eighth day following the injection, symptoms of the serum disease appeared which lasted until the twenty-sixth day. July 7th. Thirty-four days following the first injection, 1 c.c. antidiphtheritic serum injected into the left arm. The same afternoon urticaria and swelling of the lips. The next morning the arm was highly cedematous.

Alexandrine K.—Nine years old. May 28th, 1902. 180 c.c. normal horse serum. Eleven days after the injection severe symptoms appeared, which lasted until June 17th. Sixteen days following the first injection, given 1 c.c. diphtheritic antitoxic serum in the right forearm. Next morning, the hand was swollen, very painful, and smarted to such an extent that the infection was considered of an erysipelatous nature. All redness and swelling disappeared in a few days.

Elizabeth K.—Six and one-half years old. May 3d, 1902. Given 180 c.c. scarlet-fever serum. May 15th, twelve days following, sudden rise of temperature to 39.4° C. Swelling of the lymph nodes. No exanthem. Nineteen days after the first injection 50 c.c. scarlet-fever serum, following which occurred severe and painful oedema of the skin of the abdomen, which spread to the labia and thighs, and disappeared in about a week.

Franz Z.—June 6th, 1903. 1 c.c. antidiphtheritic serum. June 16th had urticaria, about nine days after the injection. August 2d, eight weeks after first injection, again given 5 c.c. antidiphtheritic serum. Shortly following, urticaria and swelling of the face.

Frieda Z.—June 10th, 1903. 1 c.c. antidiphtheritic serum. June 26th, sixteen days following, the same injection repeated and acted in all respects similar to the above case, Franz Z., her brother. On August 2d she was again given 5 c.c. antidiphtheritic serum. One hour later her face became red and swollen. The lids became so cedematous that she could not open her right eye. In two hours there was general urticaria. Temperature, 38.6° C. Moderate swelling, locally.

Elli M.—Four months old. First injection June 20th, 1904. 12 c.c. antidiphtheritic serum. Ten days later sudden rise of temperature to 39° C. and urticaria. The fever lasted two days. Eruption later became measles-like and remained several days. Nineteen days after the first injection 5 c.c. antidiphtheritic serum. One hour after this, severe general urticaria. From the site of injection, swelling of the skin of the abdomen. In

the afternoon the temperature rose to 39.5° C.; frequent vomiting.

Leopoldine K.—December 1st, 1903. 5 c.c. horse serum. Twenty-seven days following the first injection, patient received 1 c.c. antidiphtheritic serum. One hour following this last injection, definite swelling of the right hand, which later spread to the entire arm.

All these eight cases show this in common, that after the first injection of horse serum the symptoms of the serum disease appear after the normal period of incubation, namely, between the eighth to thirteenth day. But when the same individuals are again injected with horse serum after intervals of sixteen to forty-two days, there reappear at once, or at least within twenty-four hours, symptoms of the serum disease.

Von Pirquet and Schick further give a list of sixty children who were injected with antitoxic horse serum at intervals from six days to seven and a half years between the first and second injections. They found that when the second injection was given from fourteen days to four months after the first injection they obtained, with great regularity, what they termed "the immediate reaction," but when the interval between the first and second injection is over four months they obtained little or no immediate reaction, but what they termed "an accelerated reaction," for the fever, urticaria, and other symptoms of the serum disease appeared on the fifth, sixth, seventh, or eighth day. It will be remembered that the normal period of incubation for the symptoms of the serum disease to appear after the first injection is between the eighth and thirteenth day. Von Pirquet and Schick lay special stress upon the phenomena of the "immediate" and "accelerated" reactions following the second injection.

We might also conclude, despite the suggestion in our work upon sensitizing guinea-pigs by feeding them with horse serum or horse meat, that children may not be sensitized to the toxic action in horse serum by eating horse meat, from the fact that horse meat is a favorite article of diet in certain European countries, and there is nothing on record to show that the injection of horse serum in those countries is fraught with more danger than where this practice does not obtain. We must, however, remember that our work has shown that guinea-pigs are sensitized with exceedingly minute quantities of the strange proteid, and that repeated injections cause an immunity; and it is possible that the same action may be true of feeding.

Man reacts to the first injection of horse serum after a period of incubation of eight to thirteen days. Guinea-pigs show practically no reaction following the first injection. Both react to a second injection. The reactions in man and the guinea-pig, however, differ both in severity and in kind. The relation, therefore, that our observations upon the guinea-pig may have in its application to man must await further study. Of course, the fact that other animals besides man and guinea-pigs react to a second injection of horse serum would seem to indicate that we are dealing with one and the same action. We have tested monkeys, rabbits, mice, dogs, cats, rats, chickens, and pigeons to determine whether any of these animals may be sensitized to the action of horse serum. Thus far we have obtained a response in the dogs, rabbits, and cats.

Von Pirquet and Schick also found that the first injection into rabbits caused no clinical effect, but that subsequent subcutaneous injections caused immediate reaction in the production of local oedema which extended even to gangrene. Second injections, when introduced intravenously, produced symptoms of collapse and even death. Arthus also found that the injection of horse serum into rabbits caused no symptoms, whether the horse serum was injected subcutaneously or intravenously, but when he injected the serum every six days subcutaneously he obtained, after the fourth injection, oedema and local reaction which continued to gangrene.

A rabbit which von Pirquet and Schick had previ-

ously treated with eight injections was then given 2 c.c. of horse serum into the ear vein. The rabbit reacted to this in a minute and, after characteristic symptoms similar to those we see in guinea-pigs, died in about four minutes. Arthus obtained similar results with repeated injections of sterilized milk.

Hypersusceptibility and Immunity Produced by Bacterial Proteids.—Experimental studies with the bacterial proteids are of the greatest importance on account of the practical uses to which results along this line may lead. Our conviction that the phenomenon of hypersusceptibility which we have been studying in the guinea-pig has a deep significance in general pathology, especially in the problem of immunity, induced us to undertake an extensive series of experiments with proteid extracts obtained from bacterial cell masses. Some of this work is sufficiently advanced for us to record our results in part.

Hypersusceptibility may easily be induced in guinea-pigs with proteid extracts obtained from the bacterial cell. The first injection of most of the extracts used by us seems comparatively harmless to the animal. A second injection of the same extract shows, however, that profound physiological changes have taken place. A definite period must elapse between the first and second injection. The symptoms presented by the guinea-pigs as a result of the second injection resemble those caused by horse serum.

The phenomenon induced by a second injection is followed (in certain cases) by an immunity to the corresponding infection.

These results strengthen our belief that the phenomenon of hypersusceptibility has a practical significance in the prevention and cure of certain infectious processes. It gives a possible explanation of the period of incubation of some of the communicable diseases. Is it a coincidence that the period of incubation of a number of infectious diseases is about ten to fourteen days, which corresponds significantly with the time required to sensitize animals with a strange proteid? In certain infectious diseases with short periods of incubation, such as pneumonia, the crisis which commonly appears about the tenth day may find a somewhat similar explanation. It is evident that disease processes produced by soluble toxins, such as diphtheria and tetanus, do not belong to the category now under consideration.

We propose to pursue our work along these lines so as to develop this working hypothesis into possible practical results leading to the prevention and cure of certain of the communicable diseases.

Extract of Colon Bacillus.—The extract from the colon bacillus in the following experiments was obtained as follows: A two-day-old culture of *B. coli communis* in Dunham's solution was used to inoculate heavily the surface of eighty-four large agar plates. These plates were grown at 37° C. for four days and the surface growth collected. The bacterial mass was frozen forty-eight hours at about 15° F., thawed at room temperature, and then ground with sand by hand in a mortar for five hours, shaken vigorously half an hour, and again frozen eighteen hours. After again thawing, the fluid was diluted with salt solution and filtered through a Berkefeld filter. The clear filtrate gave a distinct coagulum with heat and acetic acid.

All the other extracts were obtained by a similar process. In the case of the tubercle bacillus, the bacterial mass was first washed three days in running water to eliminate the soluble tuberculin as much as possible.

The hypersusceptibility induced by the colon extracts manifested itself by symptoms resembling those already described in the case of horse serum. The guinea-pigs scratched at the mouth with their hind legs. Most of them showed evidences of respiratory embarrassment by quickened, labored, or irregular breathing. Many of the pigs lay over on their sides, which is such a common symptom. A few developed jerky movements; but in no case was convulsion noted. The pigs looked quite sick and ill at ease, but gradu-

ally recovered, so that by next morning they seemed normal.

Ten days following the second injection of the extract all the above pigs were given 5 c.c. of a heavy emulsion of colon bacillus from twenty-four-hour-old agar slants, but showed no symptoms, and remain in good condition. Three controls received the same injection and died in twelve hours.

Yeast.—The manifestations of hypersusceptibility produced by the proteid extract from yeast cells are restlessness, scratching, irregular respirations; the guinea-pigs lie down and look sick; sometimes jerky movements are seen and, in one instance, convulsions.

Anthrax.—Indications of hypersusceptibility produced by anthrax are scratching, rapid respirations; pigs frequently fall over on their sides and look sick; none of the pigs coughed or had convulsions.

A number of guinea-pigs were given the extract from anthrax bacilli before infection; some were given a single injection, some two injections, and others daily injections for twenty days. Other guinea-pigs were given the extract used as a vaccine, both in single and repeated injections, after being infected with anthrax bacilli. The extract did not seem to have any influence on the course of the disease, whether given before or after the infection.

Tuberculosis.—The indications of hypersusceptibility induced by extract of tubercle bacilli are restlessness, scratching, irregular respiration, tremor; most of the pigs lie down on their sides and look sick.

The guinea-pigs which have reacted to two injections of proteid extract obtained from the tubercle bacillus are now being tested for immunity to infection with tubercle cultures.

Typhoid.—The indications of hypersusceptibility induced by two injections of typhoid extract manifest themselves by rapid respirations; most of the pigs lie down on their sides. The symptoms presented by this series of pigs were mild.

Nine days following the second injection of the extract five pigs of the above series which had received 10 c.c. of the typhoid extract at the second injection resisted a large dose of a virulent typhoid culture. Two controls died in eighteen hours. One or two of the pigs which had received the extract were slightly sick the following day, but the next day had fully recovered and have remained so. A definite immunity was, therefore, conferred by the two injections of extract from the typhoid bacillus.

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ANEURISM, THE MATAS OPERATION FOR (Endo-aneurismorrhaphy).—The treatment of sacculated aneurisms by the method of intrasaccular suture was devised by Rudolph Matas and first practised by him in the Charity Hospital of New Orleans, Louisiana, in 1888. The case was reported and the operation fully described in the *Medical News*, October 27th, 1888. According to the author's own statement, however, he was so bound down by tradition and by the fears of atheroma and secondary hemorrhage that twelve years were allowed to elapse before he again practised his now well-known technique. Before describing this in detail, it is interesting to quote from Matas' writings that his case was the first recorded instance of the suture applied to an artery "after Hallowell and Lambert's now historic case of brachial-artery suture operated on in 1759, that is, one hundred and twenty-nine years later."

The very latest reference, however, to this question of priority has just been given by Matas. He states that further investigation has developed that Postemski of Rome, in his contribution on "La sutura dei vasi sanguigni" (an extensive research), mentions a case of accidental wound of the femoral artery, injured during operation, which he closed by a lateral arteriorrhaphy.

As this operation was performed in 1887, Postemski is entitled to the credit of the first arterial suture in man after Lambert and Hallowell. This has no immediate bearing, however, upon the fact that the application of the intravascular suture for the obliteration or cure of aneurism, both in principle and practice, is original and began with Matas in 1888; for the remarkable development in this field of vasa surgery, all of which has occurred in the past ten years, found its beginning and first stimulus in the aneurismal studies of Matas, nothing of any clinical import on the surgery of the blood-vessels having been contributed since the days of Hunter and the earlier writers.

It is, therefore, of particular interest to quote from the author of this method the following principles which underlie the application of the technique, since these are of a much further-reaching import than even the actual technique itself: "The dominant and essential features of the operation are that the aneurismal sac is regarded as a large diverticulum or prolongation of the parent artery with which it is continuous; that the lining membrane of the sac is a continuation or extension of the endothelial intima which lines the interior of the artery, and in fact of the entire vascular system, and that the sac itself, when not disturbed from its vascular connections, is capable of exhibiting all the reparative and regenerative reactions which characterize the endothelial surfaces in general when subjected to irritation. In other words, the sac, when fully formed and developed, is the analogue of the serous cavities elsewhere, not only in a histological or embryological sense, but from a surgical point of view, and it is to be treated as a serous cavity comparable to the peritoneum or pleura. This means simply that the aneurismal sac with its endothelial and serous lining will react to irritating agents in the same plastic manner that the peritoneum does when subjected to the same influences. Therefore, when the edges of the orifices, which lead from the sac to the parent artery, are brought together by a suture, we expect these surfaces to unite by the organization of the plastic exudates in precisely the same manner as the coats of the bowels are united when approximated by a Lembert suture. In other words, the dictum 'serosa to serosa,' so essential in suturing divided intestines, is

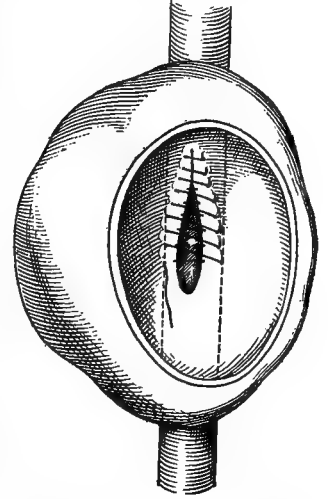


FIG. 5052.—Restorative Operation. The Lembert sutures are closing the single stoma of a sacculated aneurism.

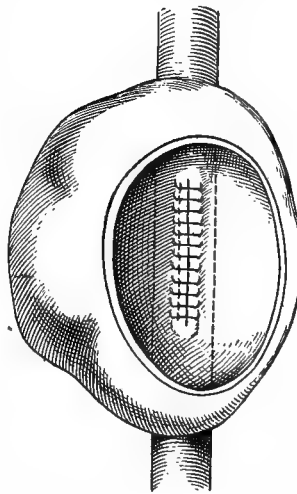


FIG. 5053.—Restorative Operation. The stoma closed.

these surfaces to unite by the organization of the plastic exudates in precisely the same manner as the coats of the bowels are united when approximated by a Lembert suture. In other words, the dictum 'serosa to serosa,' so essential in suturing divided intestines, is

simply changed in the vascular system to 'intima to intima,' in both cases the effect of the suture being the same, viz., the outpouring of plastic exudates which definitely organize [by endothelial proliferation] and unite the irritated surfaces. In order that the intima may display its reactionary and reparative qualities to the best advantage, it is necessary that its vitality or nutrition be unimpaired by separating or detaching it from the tissues in which it is embedded, and upon which its vascular supply depends. The sac, therefore, should only be opened or incised, never dissected away from its surroundings as is necessary to do when the old Antyllian operation or the extirpation of an aneurism is attempted.⁵

Morphology of Aneurism Favorable to Operation.—

As is well known, there are two classes of aneurisms: those in which the "aneurismal sac is simply attached, as it were, to its parent artery at a single orifice, the artery retaining its calibre and continuity throughout its course and communicating with the aneurismal sac only by a small opening in its walls," and those in which

ture has permitted the aneurismal sac in a very considerable percentage of the cases to be obliterated without interrupting the continuity of the parent artery. (Matas' personal communication.)

In the other and more frequent type of aneurism, the

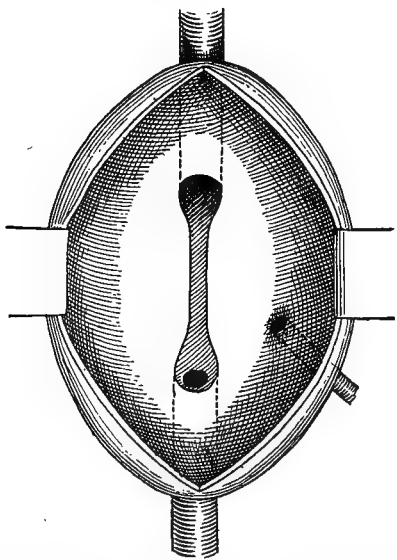


FIG. 5054.—Reconstructive Operation. Sacculated aneurism opened and seen from within. Note the opening of a collateral to one side of the main stomata.

sac and vessel are integrated. In the first class it is evident that if the opening which connects the sac with the main artery is closed by a suture, the sac will be obliterated, i.e., the aneurism cured, without interfering with the arterial current that flows in the artery connected with it. In these cases the ideal surgery is readily accomplished. By preserving the lumen or the continuity of the parent artery, this method challenges the infallibility of Scarpa's dictum, which has remained an immutable and unshaken postulate in surgery from the time it was first enunciated by that remarkable surgeon and thinker, over one hundred years ago. According to Scarpa, "It is a certain and incontrovertible fact in practical surgery that a complete and radical cure of aneurism cannot be obtained in whatever part of the body this tumor (aneurism) is situated, unless the ulcerated, lacerated, or wounded artery from which the aneurism is derived is by the assistance of nature, or by nature combined with art, obliterated and converted into a perfectly solid ligamentous substance for a certain space above and below the place of the ulceration, laceration, or wound." This postulate, so thoroughly confirmed by the experience of surgeons throughout the centuries, is no longer tenable as an absolute truth, since the substitution of the suture for the liga-

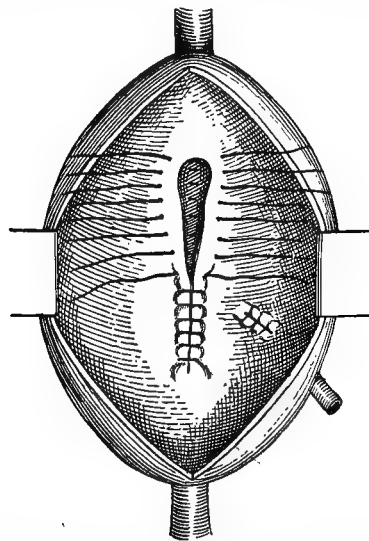


FIG. 5055.—Reconstructive Operation. Aneurismal sac shown in Fig. 5054. Stomata partly closed by Lembert sutures.

sac is an expansion of the artery, not only involving all the walls of the vessel, but a part of its continuity for a greater or lesser portion of its length. Such aneurisms, when opened, present two main openings the obliteration of which cannot but stop the distal circulation of the blood current. Considerable misapprehension has been evidenced, particularly in Europe, as to the necessity of attempting to preserve the continuity of the artery in every case, many reviewers having erroneously held this to be the ultimate aim of the operation. Matas stated that as the result of a study of the collective experience of American surgeons, the European operators in general having misinterpreted the technique so far as to render their reports relatively valueless, it is safe to conclude that the preservation of the continuity of the vessel is not essential to success in the majority of the cases, being indicated positively only in sac-ciform aneurisms and as a provisional measure in some of the fusiform variety. The very essence of endo-aneurismorrhaphy in the fusiform type depends upon the preservation of the saccular and perianeurismal collateral circulation, which is preserved in the Matas technique, rather than upon the preservation of the

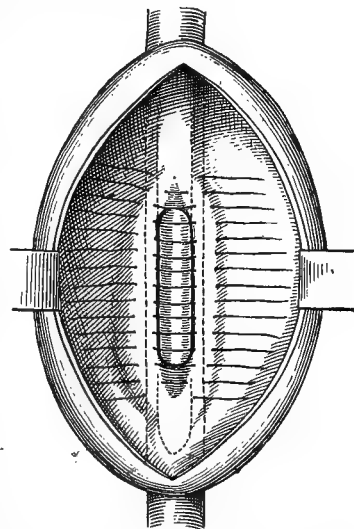


FIG. 5056.—Reconstructive Operation. Catheter in situ.

the

lumen of the artery. The point to make clear is that the advantage of the Matas operation, as applied to fusiform aneurisms, over other methods, lies in the preservation of collateral circulation around the undisturbed and undissected sac walls, and through these the collaterals of the circulation of the extremity, after the tension of the sac has been relieved by the complete evacuation of its contents. Herein, and not in the making of a new canal through the sac, lies the meat of the Matas cocoanut.

It is evident, therefore, that the artery may or may not be obliterated according to the morphology of the aneurismal sac. Based upon this, endoaneurismorrhaphy is divided into three varieties: (1) Obliterative, (2) restorative, (3) reconstructive. The first is indicated in all fusiform aneurisms in which there are two or more orifices of supply and in which the parent artery is entirely lost at the seat of the aneurism. No attempt is here made to restore the continuity of the artery, dependence for distal circulation being placed upon the relief of all perianeurismal tension by the complete evacuation of the sac and by the undisturbed collaterals of the sac wall. Of the sixty-six operations by the

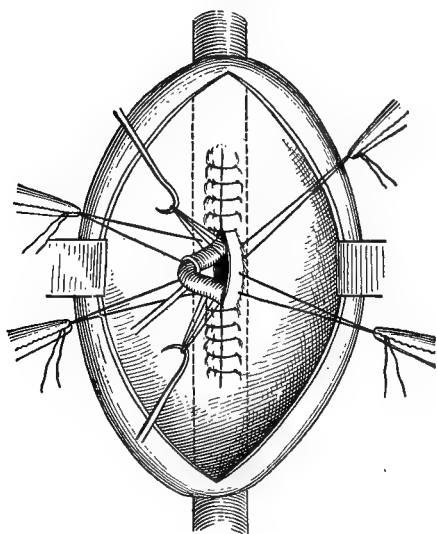


FIG. 5057.—Detail of Reconstructive Operation. The catheter is being withdrawn.

Matas method, forty-two are of cases illustrating the obliterative technique. The efficiency of the collaterals is proven by the absence of postoperative gangrene in all uncomplicated cases in which the satellite vein has not been injured.

Restorative endoaneurismorrhaphy is applicable solely to the treatment of sacciform aneurisms. The sac is simply opened, complete hæmostasis being maintained, the clot is washed out, the openings closed, and the blood supply of the sac lumen permanently arrested. The endothelial surfaces of the sac are then brought together and the wound is closed in the manner shortly to be described. Nine operations of this type have been described.

Reconstructive endoaneurismorrhaphy is obviously applicable solely to the treatment of fusiform aneurisms in which there has been little or no dissecting of the coats of the sac and in which the two openings lie on the same level and are readily accessible. The continuity of the main artery may in these chosen cases be restored by autoplasmic suture of the base of the sac over a catheter which may be inserted into the proximal and the distal opening. This guide should be removed before the last suture is tied. Then the technique of obliteration of the main portion of the sac is carried on

as in the other variants of the operation. Fifteen cases of this type of operation have been reported. This reconstruction is the least important factor in the Matas technique.

Anatomical Essentials for the Success of the Operation.—First, the aneurism should be so situated that

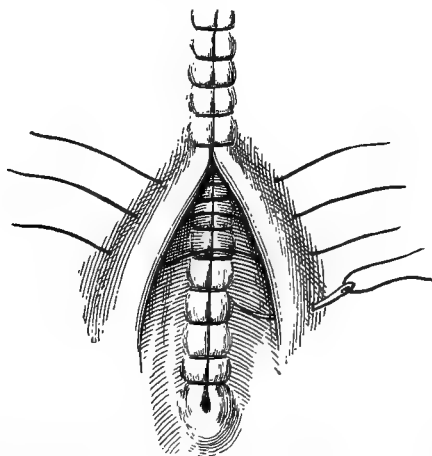


FIG. 5058.—Obliterative Operation, Showing Insertion of Second Row of Sutures.

provisional hæmostasis may be obtained by controlling the proximal arterial supply of the tumor on the cardiac side. In regions where the Esmarch bandage cannot be easily applied, great care must be exercised in securing the distal as well as the cardiac side of the main trunk. Second, a free opening of the sac in its longitudinal axis without dissecting its walls or disturbing unnecessarily its relations with the surrounding tissues in which it is embedded, especially avoiding the accompanying veins and nerves. This, as already stated, secures the advantages of collateral blood supply and marks the difference between the new operation and the old. Third, all the orifices which open into the sac are exposed to view so that they may be sutured just after the manner of intestinal wounds. The operation is thus simply a further application of the sur-

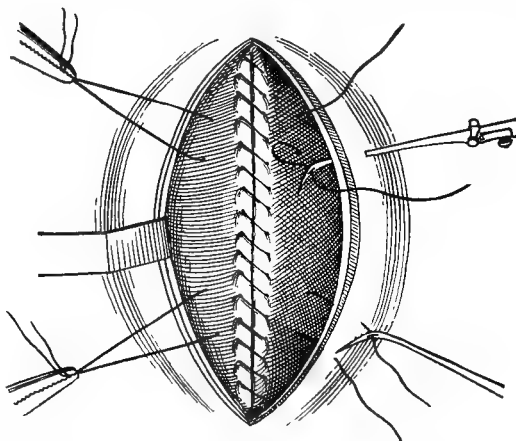


FIG. 5059.—Detail of Imbricating Stitches for Obliteration of Dead Spaces.

gical truth that hemorrhage should be controlled and sutured at its point of exit from the vessel—never in continuity.

Technique.—Matas prefers absorbable chromic gut (fifteen-day). He formerly used silk. Any good intestinal needle will serve the purpose. In all cases he

prefers the continuous suture, for it approximates the edges, not only more rapidly, but more securely. As to the number of stitches, he states that no less than eight to ten suture points to the inch should be employed. The needle should penetrate at least one-fourth to one-sixth of an inch beyond the margin of the orifice, reappearing on the opposite margin as in the start. After the closure of all openings into the

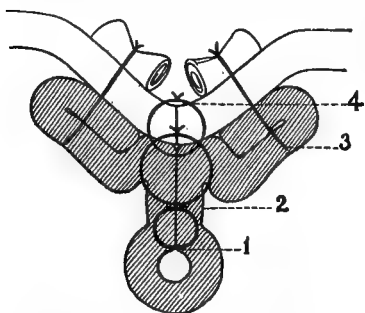


FIG. 5060.—Cross Section of the Tissues, Showing Imbrication in the Reconstructive Operation.

of the relief of blood pressure upon the sac wall. They are brought together in the middle line by a continuous suture. This is superimposed upon the first line of hæmostatic sutures and not only serves to reinforce them, but to raise the floor of the sac. This technique may be repeated and a third layer placed over the second if sufficient tissue be present. The base of the sac is thus brought up nearly to a level with the skin, which is then carried down and sutured upon it. In the treatment of small sacs, the walls may be brought together by a row of continuous absorbable sutures, which bring the endothelial surfaces in complete apposition. In certain large adherent popliteal aneurisms, for example, the folds referred to frequently do not form. In these cases all that can be done is to narrow the cavity as much as possible by inverting and tacking fast to the bottom and side the relaxed skin flap. Obliteration of the sac by infolding is occasionally impossible. In these rare cases it may be left to heal by granulation, or recourse may be had to skin grafting. In general the technique of closure of the sac may be enumerated according to Matas, as follows: "First, do not suture too frequently or too tightly lest the circulation of the sutured tissues be impaired. Second, appose the sides of the wound as closely as possible so that plastic union rather than granulation may close the wound. Third, drain all cavities which are too large or irregular to be apposed."

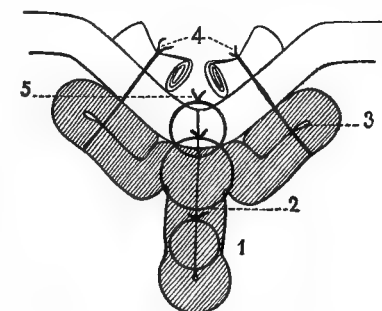


FIG. 5061.—Cross Section of the Tissues in the Obliterative Operation.

Advantages of the Technique.—(1) Its simplicity reduces traumatism to a minimum. (2) Its safety, which depends, as already noted, upon the non-interference with collateral circulation about the sac or with important perianeurismal veins, nerves, or other organs. (3) Its complete relief of perianeurismal pressure effect by immediate evacuation of the sac contents. (4) Its permanency as a cure.

Statistical Results.—The intrasaccular-suture method has been applied up to the present writing (December 10th, 1907, so far as the author has been able to collect the same), 66 times by 34 different operators, 33 American and 1 European (Lozano of Spain). Other cases (arterial and arteriovenous) have been reported in which the suture has been applied to close wounded arteries in traumatic false aneurism, but these are not included in the statistics because they are not morphologically relevant. These cases are classed as atypical arteriorrhaphies and not as aneurismorrhaphies.

The 66 aneurisms involved the following arteries: Popliteal, 39; femoral, 15; post-tibial, 1; inguinal (iliofemoral), 1; axillary, 1; brachial, 2; subclavian, 2; subclavio-axillary, 1; external carotid, 1; gluteal, 1; abdominal aorta, 2. Of these, 42 were obliterative operations, 9 restorative, and 15 reconstructive. Of the popliteal aneurisms 22 were treated by the obliterative, 6 by the restorative, and 11 by the reconstructive method. Of the femoral aneurisms, 10 were obliterative, 3 restorative, 2 reconstructive operations.

In the 66 cases there were 4 deaths; these occurred in obliterative cases, 2 abdominal aortic caused by shock and hemorrhage, both very unfavorable cases from Matas' point of view. In both, however, the openings in the sac were sutured and the sutures held, but hemorrhage occurred above the aneurism from the damaged calcareous coats of the artery, compelling the operator to leave clamps *in situ*. One popliteal was complicated by tetanus and gangrene; in this case the vein was also injured and had to be ligated.

One femoral, in a subject of multiple aneurisms, in which a second iliac formed and ruptured where a traction loop had to be applied for prophylactic control while operating upon the first-found aneurism.

Total gangrenes, 3; all after obliterative operations. The leg became gangrenous in two popliteal cases; in one the patient died from tetanus, in the other after amputation. In both cases the popliteal vein was injured and had to be tied in the course of the operation. In one femoral, gangrene from embolism or thrombosis in the popliteal artery at the bifurcation far beyond the aneurism; amputation of the leg and recovery. No secondary hemorrhage and no relapses have been reported in the obliterative cases.

In two cases gangrene already existed in the toes and feet when the patient applied for treatment. The aneurisms were undergoing spontaneous obliteration by thrombus formation in the sac. The obliterative operation was performed in both cases with the hope of improving the collateral circulation and reducing the perianeurismal tension in the popliteal space. Both patients recovered after conservative amputations of the leg.

To summarize: Obliterative endoaneurismorrhaphy, 42 cases—popliteal, 22; femoral, 10; subclavian, 2; subclavio-axillary, 1; brachial, 2; external carotid, 1; gluteal, 1; posterior tibial, 1; abdominal aorta, 2. Deaths, as previously explained, 4, viz., 2 abdominal aortic, 1 femoral, 1 popliteal; in none of them was death due to any inherent defect in the method itself, but to accidental conditions; gangrene, 3 cases, viz., 2 popliteal; 1 femoral. Secondary hemorrhage none. Relapses none.

Restorative endoaneurismorrhaphy, 9 cases: 6 popliteal, 3 femoral; all sacciform aneurisms. No deaths; no gangrene; no relapses; several over two or three years since operation.

Reconstructive endoaneurismorrhaphy, 15 cases: 11 popliteal, 2 femoral, 1 inguinal, 1 axillary. Deaths none; gangrene none; relapses 2, and 1 too recent to state the outcome. The relapsed cases were 2 popliteal. In one the patient preferred amputation to another operation; in the other the sac was reopened and the orifice closed by the obliterative procedure with permanent success. The inguinal case, though apparently very simple at the time, is still too recent to be classed as a permanent success.

Again, to sum up, we find 66 cases of all types, with 4 deaths (6 per cent.), in none of which was the fatal outcome due to defects inherent in the method itself. Gangrene 3 (4.5 per cent.), also from causes which are not to be closely attributed to the method, viz., injury and ligation of the satellite vein; embolism or thrombosis in the periphery subsequent to operation and at a distance from the seat of the aneurism; and 2 positive relapses in the reconstructive operation.

J. W. Draper Maury.

ANTHRACOSIS.—The truth of the universally accepted theory that anthracosis of the lungs is an aërogenous condition due to the inhalation of air containing carbon dust has been vigorously attacked during the last several years. The foundations upon which our older belief rested have been so shaken by the work of Calmette and his colleagues that we find ourselves in the interesting position of doubt concerning the origin of one of the most familiar and trite pathological conditions, the inhalation origin of which we have accepted in the past without question. Through the investigations of Calmette, Guérin, Van Steenberghe, and Grysez, the opinion has gained ground in France that the deposits of carbon dust in the lungs and bronchial glands are the results of *ingestion* and not of *inhalation*. Experiments on rabbits showed that ligation of the œsophagus prevented anthracosis; while, when swallowing was permitted in animals having one bronchus plugged with cotton-wool, the corresponding lung developed anthracosis in the same degree as the other lung. Repeated experiments by the investigators named have shown that finely powdered coal dust, cinabar, and India ink may pass the intestinal wall into the lymphatic system and thence into the lungs and bronchial glands. The intestinal epithelium apparently plays no part in the transmission of the dust particles; it is accomplished chiefly or wholly by the leucocytes. In young animals the pigment thus taken in through the intestinal mucosa is largely filtered out by the mesenteric glands, but in older animals a larger portion of the dust or pigment particles passes on through the thoracic duct and thence into the lungs. Feeding experiments show that pulmonary anthracosis may develop rapidly in this way. Calmette argues, therefore, that physiological anthracosis is chiefly due to an ingestion of carbon dust. Only after a prolonged stay in a very smoky atmosphere does inhalation play an important rôle in the production of this condition.

Biondi has confirmed Calmette's statements in so far as experiments with powdered graphite are concerned, but points out that metallic dust acts in a very different way from carbon dust. When ingested the former is dissolved or chemically changed and is not deposited in the lungs or bronchial glands, so that deposits of metallic dust occurring in the lungs must be the results of inhalation. Petit has also confirmed Calmette's views by the feeding of charcoal dust to infants suffering from fatal conditions such as tuberculosis and marasmus. To prevent the entrance of any of the dust into the respiratory tract it was given in a suspension through an œsophageal tube. At autopsy the mesenteric glands, lungs, and bronchial glands of the tuberculous infants showed anthracosis, but it was absent in the glands of the marasmic infants.

In Germany the tendency has been to discredit the work of the French observers. Schultze found in feeding experiments carried out upon guinea-pigs and rabbits that deposits of the pigment were present only in the intestine and lung, and regards this as evidence that some of the carbon dust had been inhaled accidentally. Aschoff's experiments with the feeding of carmine were negative. Miranescu in a series of feeding experiments with India ink, carmine, and charcoal emulsion obtained no pulmonary deposits as the result of ingestion alone. Likewise the feeding experiments conducted by Feliziani proved negative. On the other hand, inhala-

tion experiments carried out by Bennecke upon the guinea-pig, rabbit, and dog showed that inhaled carbon dust can penetrate the lungs and after entering the lymphatics pass to the bronchial glands.

In this undecided state the matter stands at the present time, and a thorough investigation of the whole subject of anthracosis seems necessary in order to settle this and the other important questions arising out of Calmette's claims. If the ingestion theory of anthracosis is shown to be correct, it would appear not at all improbable that many of the inflammatory affections of the lung, as well as tuberculosis, are the result of infection by way of the intestinal tract.

Other recent contributions to our knowledge of anthracosis deal with its relation to tuberculosis. Among these may be mentioned Ribbert's view that anthracosis is largely determined by a previous healed tuberculosis, although he rejects wholly the ingestion theory. Wainwright and Nichols have carried out experimental investigations to determine if pulmonary anthracosis rendered the lungs less susceptible to tuberculosis, as has been claimed is the case with miners. Two sets of guinea-pigs were given intratracheal injections of tubercle bacilli. One set had been kept for two months in an atmosphere saturated with coal dust. In this group of animals the lungs remained practically free, although abdominal tuberculosis developed. The control group developed pulmonary lesions. No satisfactory explanation of this phenomenon was discovered, but it was thought that the soluble salts of lime contained in coal might have an inhibiting action upon the growth of tubercle bacilli, or that certain changes occur in the structure of the lungs that render them less susceptible to infection.

Aldred Scott Warthin.

ARSENIC, POISONING BY.—Knowledge of the poisonous nature of arsenic seems to have come from out the mysterious East. Long before the dawn of written history the Asiatics, the Egyptians, and doubtless other Eastern peoples, seem to have been well acquainted with the sulphides of arsenic and probably also with the method of preparing the trioxide by roasting arsenical ores. The oldest of the manuscripts and papyri dealing with *materia medica*, etc., which have come down to us (the famous Leyden collection), include the name "arsenic" in the list of substances with medicinal or poisonous action. We are ignorant, however, of the part this substance played in the world's drama prior to the first century A.D. But about this period the writings of Dioscorides and of Olympiodorus caused the method for the preparation of the oxide to be well known and its poisonous property to be well understood. From this time on, arsenic trioxide, because of its being colorless, odorless, tasteless, and insidious in its action, became a factor in history. Professional poisoners soon appeared on the stage and succeeded in developing poisoning into an art—if this be not a prostitution of this term. The first of these artists in crime seems to have been Locusta. Attached to the court of Agrippina she caused the death of Claudius by means of arsenic; later, as the tool of Nero, she accomplished the death of Britannicus and threw Rome into consternation and terror. Put to death by Galba in 68 A.D., she was succeeded by an adept disciple, Canidia, who administered arsenic to a large number of victims. From this time on, Italy proved a hotbed for schools of crime in which arsenic was always the chief agent. Until the thirteenth and to a certain extent to the fifteenth century, murder by means of arsenical preparations knew no bounds and overflowed all Europe. Standing forth among the many historical lesser criminals, we have Charles the Bad, King of Navarre, whose remarkable letters patent (fourteenth century), giving directions for the poisoning of his brothers and uncles by means of white arsenic to be mixed with food or wine, are still extant; the Pope Alexander VI., murdering out of revenge those of his cardinals who disagreed with him, and the wealthy cardinals, his friends, in order that he might seize their property, meeting death himself through the

mistake of a servant who gave him a bottle of wine containing arsenic intended for Cardinal Corneto. Alexander left two of his five children, Lucretia and Caesar Borgia, of hideous memory, demons in human form, to distribute arsenic in all directions. About this time arose the famous Council of Ten of Venice, spreading murder abroad largely through the agency of an adept in the use of arsenic, de Ragubo, the Franciscan.

A century later makes us acquainted with the celebrated "Acqua Toffana," which probably consisted of a solution of arsenic trioxide in aqua cymbalaria, to which a small amount of tincture of cantharides was added. The woman Toffana, living in Palermo and Naples, discoverer and dispenser of this liquid, is credited with the death of over five hundred victims, including several crowned heads and two popes. While she practised her nefarious trade for years unsuspected, the Acqua Toffana struck terror throughout all Italy, and even throughout France and Austria. After her detection she fled for safety to a convent, where for twenty years longer her horrible trade flourished in secret. Upon her final detection and execution La Toffana's clients were supplied with the arsenical fluid by Spara, who had obtained the secret of its preparation from Toffana. Spara sold her preparations under a variety of other names, as, for example, "Manna di S. Nicolas di Bari," "Acquetta di Napoli," etc. Since Spara's clients seem to have been mostly of the middle class, records are lacking as to the extent of her criminal practices. Toffana and Spara also prepared and dispensed another poison even more potent, in which arsenic was combined with putrefactive compounds (the arsenical ptomaines of Selmi). This preparation, sold under the name of "Acquetta di Perugia," was prepared by sprinkling the viscera of a freshly killed pig with white arsenic, hanging them up and then collecting in a vessel the drippings of the putrefying material.

France now became the theatre of the great arsenical crimes of history through Catherine de Medici, who brought with her to France arch poisoners from her native land. The court of Louis XIV. was fairly smothered in crime. Among the hundreds of petty poisoners two remarkable women, doubtless the greatest criminals France has ever seen, stand head and shoulders above the rest. The first of these, Marguerite d'Aubray, Marquise de Brinvilliers, angelically beautiful, with winning voice and saint-like appearance, yet addicted to unspeakable vices from a child up, had been taught the methods of mixing arsenic with foods and beverages by her paramour Saint Croix. This woman had set her heart upon inheriting the family estate, and to gain her end it became necessary to cause the death of her father, brothers, and sister. In order to accomplish this she obtained entrance to the great hospitals of Paris under the guise of a Sister of Mercy. Here as a nurse she administered arsenic with food and medicine, noted the effects, going each day to the internes to learn the progress of the disease. Finding that her practices were unsuspected and undetected, she carried her experiments still further by giving arsenic in food to the poor who called at her door, dosing her servants and visiting the hospitals to which they were taken in order to learn the effect. Having at last satisfied herself that she knew the dose and the rate at which the poison should be administered, she proceeded with the execution of her long-planned crime. During a period of over eight months she administered arsenic to her father, thirty times by her own hands and a number of times by a servant. At the end of this period the murder was accomplished by giving a double dose. In a like manner she disposed of two brothers and attempted the life of her sister. If her servants displeased her, a little arsenic, carefully dispensed, put them out of her way. It has been impossible to ascertain the number of her victims, so cunningly did she work. Not only did she use arsenic trioxide alone, but also a carefully compounded mixture of this substance with mercuric chloride. Her crimes being discovered upon the death of Saint Croix, she was tried, found guilty, and executed in July, 1676. Thus it was that

the Marquise de Brinvilliers invented the infamous "poudre de succession," which in the hands of the second of the women, La Voisin and her accomplices, literally powdered Paris and part of France with arsenic.

The revolting story of La Voisin is foreign to the topic under discussion. Suffice it to say that the poison she dispensed was generally white arsenic; but what is noteworthy, is that she followed the de Brinvilliers' method, which had been experimentally developed, namely, slow poisoning. Poisoning became such an epidemic in France, following the publicity of these cases, that the notorious special court (La Chambre ardente—Court of Poisoners) was established. This body proceeded so perseveringly, thoroughly, and mercilessly that since 1682 there have been no systematic poisonings by professional poisoners, clubs, or bands. It has been recently stated that in modern times no Locusta, Toffana, nor de Brinvilliers can exist, that the illness of the victims would promptly be diagnosed as arsenical poisoning and the criminal discovered. Unfortunately, this belief is not justified, for there are many cases which demonstrate that slow poisoning by arsenic is not readily diagnosed. Take, for example, the case of the monomaniac Hélène Jegado, who from 1833 to 1852 poisoned some 47 persons, about 30 of whom died, all of arsenic poisoning; or again there is the woman Van der Linden, who in 1887, acting as a nurse and at the same time agent for an accident insurance company, poisoned, or attempted to poison, 103 persons. Twenty-seven died; 47 were made seriously ill. As a nurse she dosed her victims, in whose names she herself had made out policies. In due time she collected from the company the amount of the policy for illness or death. So carefully did she proceed that the illness of her victims was not diagnosed as arsenicism. Again, take the cases of great mass-poisoning by wine containing arsenic at Hyères in 1887, due to the circumstance that a wine merchant, with the intention of plastering his wine, had dropped into the fermentation vat by mistake a quantity of white arsenic. There were over 400 victims and 4 deaths. All sorts of diagnoses were made by the physicians, and it was not until many months afterward that the true cause was discovered. Similar errors were made in 1900-02 in the famous beer poisonings in Great Britain. In this epidemic there were over 4,000 victims and 300 deaths. The first cases of illness were reported in the latter part of April and early in May, but it was not until the following November, seven months later, that the proper diagnosis of arsenical poisoning was surely established, and it was shown that the trouble came from impure sulphuric acid used for the inversion of sugar and starch, which materials under the Gladstone bill could be used for the manufacture of beer.

Within a few months two cases of slow poisoning by arsenic have come to the author's attention, in each of which the attending physician failed properly to diagnose the illness. One of these cases was homicidal.

The lessons to be drawn from the historical cases and others cited above seem quite plain. The physical diagnosis of subacute or chronic arsenical poisoning is often uncommonly difficult.

MOST IMPORTANT COMPOUNDS WITH REFERENCE TO POISONINGS.—*Arsenic trioxide*, As_2O_3 (synonyms: arsenious acid, arsenious anhydride, white arsenic, arsenic, ratsbane, rough-on-rats, etc.) exists in two allotropic modifications, the amorphous and the crystalline. The crystalline form is of a dead white, opaque, and porcelain-like appearance; the amorphous, on the other hand, is clear, transparent, and glass-like, and for this reason is often termed vitreous, and has a tendency to pass slowly into the crystalline state. Because of this change, commercial samples of lump white arsenic are mixtures of the two modifications. Save in India, where it is sometimes colored yellow with cow's urine, arsenic trioxide occurs in commerce as a heavy white powder, or in the form of opaque white lumps, which when broken show a transparent glassy centre. The solubility of the commercial samples varies within quite wide limits; this is due to the fact that the solubility of the two modifica-

tions of As_2O_3 are different, that of the pure crystalline being about 1 in 350 of water at 15°C ., and that of the pure amorphous 1 in 108. Cooled from boiling, 1 part in 45 of the crystalline remains in solution and 1 part in 30 of the amorphous. No two observers agree, however, as to the solubility of As_2O_3 .

Arsenites.—All the samples of commercial dry arsenite of sodium and of potassium which have been examined by the author seem to correspond most closely to the formulas NaAsO_2 and KAsO_2 . Their solubility in water is quite variable, but is always much greater than that of the trioxide. The majority of cases of poisoning from alkaline arsenites have been from the medicinal preparations of these salts, such as Fowler's solution, etc. Only a very few of these cases have been criminal.

Arsenates.—These salts correspond to the general formula R_3AsO_4 . They are of little toxicological interest save for the fact that arsenic acid has been largely used in certain industries (e.g., manufacture of aniline dyes) as an oxidizing agent, and the products placed on the market in an impure condition contain arsenic in enormous quantities.

Sulphides of Arsenic.—The disulphide, As_2S_2 , occurs in nature as realgar, and was known to the ancients under the name sandarac or sandaracque. Realgar, both the mineral and the artificial compound, has been used as a pigment, in pyrotechnics, etc. The trisulphide, As_2S_3 , long known as the mineral orpiment or auripigment, has had a variety of commercial uses. It was formerly used in printing, in tanning as a depilatory, in medicine, as a pigment, etc. The pentasulphide, As_2S_5 , is of no medicinal importance. All the sulphides met with in commerce are amorphous yellow powders, varying in color from a light lemon yellow to a deep golden or even orange tint. When pure they are insoluble in water, hence their toxicity is very low. Some authorities hold that the pure sulphides are not poisonous. Experimental evidence shows, however, that these compounds are acted upon by the fluids of the body, and that arsenic is resorbed. Doubtless a long sojourn of these sulphides in the alimentary canal would lead to serious results. The commercial sulphides are invariably violent poisons, since they contain arsenic trioxide, sometimes to the extent of as much as thirty per cent. Le Prince and Chabenat report the case of a young girl who used an ointment consisting of 65 parts of butter and 35 parts of orpiment as a dressing for a tumor of the breast. Acute arsenic poisoning resulted, with death on the fifth day after the application of the dressing. As a depilatory, orpiment has been used from earliest times. It was a mixture of orpiment with lime or chalk, which was used by the ancients for the removal of the pubic hairs—a practice said to be still extant, at least in the case of women, in certain Mussulman tribes of the East.

Cases of poisoning from organic compounds of arsenic have not yet been reported, if we except those due to the notorious Acquetta di Peruzia. But considerable experimental work has been done on animals with kacodyl, kacodylic acid, diphenylarsine, monophenylarsine, arsenodimethylcyanide, etc.

Coloring matters, pigments, containing arsenic, are responsible for a large percentage of cases of poisoning, both acute and chronic. Scheele's green (synonym—mineral green, Swiss green) is copper arsenite of somewhat variable composition. It is insoluble in water, and corresponds to the formulas CuHAsO_3 or $\text{Cu}_3(\text{AsO}_3)_2\cdot 2\text{H}_2\text{O}$. This beautiful compound is used as a pigment in painting, printing, etc., and as an insecticide. Paris green (synonyms: Vienna green, mitis green, Schweinfurter green) is a double salt, copper aceto-arsenite, corresponding to the formula $\text{Cu}(\text{As}_2\text{O}_4)_3\cdot \text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_2$. The commercial product is of variable composition according to the method employed in its manufacture. It is now used in enormous quantities as an insecticide; rarely as a pigment in painting, coloring, etc. Aniline dyes of the rose-aniline group, which have been made by the old arsenical process, usually contain arsenic in large amount. The most important of these are the magentas and reds, but

the blues, violets, purples, etc., may also be arsenical. In fact, it may be said that there is scarcely a shade which cannot be obtained by blending arsenic-containing dyes. Practically all the manufacturers of aniline dyes have now abandoned the arsenical process, but the author is informed that there is still one firm in New York State that uses arsenic acid in the preparation of fuchsin. Closely related to the aniline dyes are the arsenical lakes, such as Cochineal red, Vienna red, etc. King's yellow consists of impure arsenic trisulphide, hence is essentially orpiment. It often contains eighty to ninety per cent. As_2O_3 . Mineral blue, a pigment in which copper arsenite and potassium arsenite enter in about equal parts, contains about thirty-nine per cent. arsenic.

Arsenical insecticides are responsible for a large number of deaths, accidental, suicidal, and criminal. Of these substances the most important is Paris green. Its composition and quality are now controlled by statutory enactment in several States of the Union. When sold as an insecticide the statutes call for a product containing combined arsenic in an amount which shall be not less than fifty per cent. calculated as As_2O_3 , not over four per cent. of which shall be soluble in cold water. Most of the cases of poisoning by this material occur in the United States and in Russia. London purple (synonyms: English purple, Paris purple), formerly much used, is obtained by treating a by-product of the aniline dye industry with lime. The arsenic is present both as calcium arsenite and as calcium arsenate, the latter in excess of the former. Calculated as arsenic the average amount present in London purple is about twenty-nine per cent. Arsenoids, substitutes for Paris green, have been placed on the market in recent years. Green arsenoid contains on an average about sixty per cent. As_2O_3 , and has been incorrectly called Scheele's green. White arsenoid contains barium arsenite; thirty-three per cent. of the arsenic present is water-soluble. Para green is a mixture of Paris green with about thirty-six per cent. gypsum. Laurel green consists essentially of calcium arsenite (thirteen per cent.), gypsum, calcium carbonate, and magnesium carbonate.

Vermis Killers.—Of the many arsenical poisons on the market for the purpose of destroying rats, mice, etc., only one needs discussion, i.e., rough-on-rats. This preparation has been employed in many crimes in the United States and consists of arsenic trioxide about seventy-two per cent., barium carbonate twenty-six per cent., sand two per cent., with usually a little carbon to color it. In case of a question of poisoning by this vermin killer, barium should always be searched for. The author has, however, in his possession a sample of this material purchased some years ago which contains no barium.

Arsenic in Foods, Beverages, etc., occurs (1) as a preservative, (2) in coloring matter added, or (3) as an accidental impurity. In official reports issued by the German Government the claim is made that there are annually exported from the United States to European ports enormous quantities of dried apples which have been treated with weak arsenical solutions to preserve them from decay and from the attacks of insects. Moscow, Russia, suffered severely some years ago from a cholera-like epidemic, the cause of which was eventually traced to sturgeon flesh which had been sprinkled with white arsenic to arrest decomposition. The addition of arsenical colors to foods and beverages has given rise to a large number of cases of arsenical poisoning. Sausage, jellies, preserved fruit, wines, fruit syrups, confectionery, cakes, etc., have all been found to have caused trouble. Usually this has been due to arsenical aniline dyes, but in a few instances Paris green has been present. Accidents arising from the presence of arsenic as an impurity in some product used in the manufacture of the food or beverage are usually confined to beers, ales, or glucose preparations. While we are considering poisonous food materials, the fact must not be overlooked that cattle feeding in the neighborhood of industries throwing out arsenic may become poisoned or else relatively immune from

habitual use, and their flesh when eaten by man may lead to very serious results. The same holds true for milk secreted by an animal which has taken arsenic into its system.

Arsenic in Colored Papers, Inks, Clothing, etc.—Many cases of very serious chronic arsenical poisoning have been traced to these sources. A decade ago the amount of highly arsenical wall papers was appalling, and in spite of the denial of eminent chemists and hygienists, the evidence is such that chronic poisoning from arsenical wall papers must be accepted as an established fact, providing that the room so papered is small, damp, and ill ventilated, and the alleged victim spends much time in the room. Contrary to popular opinion, green-tinted papers are rarely arsenical; those which have caused trouble in the United States have almost invariably been tinted in shades of red. In an investigation conducted by the author some years ago upon an undoubted case of arsenicism from wall paper, it was found that over ninety per cent. of the red and maroon papers obtainable of the same date of manufacture as that on the walls of the room were highly arsenical. Many samples of wall papers manufactured within the last six years have since been examined, but none of these modern papers have thus far been found which contain more than mere traces of arsenic. In all probability the cause of arsenicism from wall papers is largely due to the formation, by moulds and bacteria, of arsine and of a volatile organic arsenic compound. This peculiar action is so well marked in the case of *Penicillium brevicauda* that advantage is taken of the fact for the purpose of testing for the presence of arsenic. *Mucor mucedo*, *Aspergillus glaucus*, *Aspergillus virescens* also possess this same property, but to a less degree. Colored papers other than wall papers have also given rise to poisoning: as, for example, the chewing of such papers by children, the moistening with the tongue of many colored gummed labels. In 1889 several cashiers in German banks were poisoned through handling with moistened fingers large numbers of Swiss banknotes printed with arsenical ink. Several cases are on record of poisoning from using copying inks, typewriter ribbons and indelible pencils made with arsenical aniline dyes. Graffsky has described several very serious cases of chronic poisoning from handling colored chalk in one of the schools of Germany. A violet-colored crayon was found to contain over seven per cent. arsenic. Clothing dyed with impure aniline colors has been the cause of many a sad case of illness. These cases have usually been caused by such wearing apparel as comes in direct contact with the skin, such as stockings, trousers, waists, etc. In Germany copper arsenite has been used for coloring tarlatan and several cases of serious poisoning have resulted therefrom. Two of the most striking cases of arsenical paralysis with which we are acquainted were due to green tarlatan ball gowns. Zinreck states that he found in twenty yards of this material used for a ball gown 300 gm. of Paris green.

Medicinal preparations have given rise to poisoning, either from overdosage or because of the presence of arsenic as an impurity in the substance administered, as, for example, in bismuth subnitrate and other bismuth preparations, sodium phosphate, glycerin, chloroform, phosphoric acid, sulphuric acid, etc. For the composition and dosage of arsenical medicines, see *Arsenic*, Vol. I., of REFERENCE HANDBOOK.

Industrial poisoning by arsenic is by no means rare, for in a large number of industries the workmen are exposed to compounds of this element in one form or another. In the following table will be found a list of trades or articles manufactured which are credited with cases of arsenicism, and a brief statement of the cause of the illness.

Name of Industry or Article Manufactured.	Causes of Poisoning.
Paints in which the basis is orpiment, copper arsenites, mineral blue, etc.	Arsine, arsenical dust.
White enamel glass, stained glass and certain other glasses.	Arsine, arsenical dust.

Name of Industry or Article Manufactured.	Causes of Poisoning.
Copper, cobalt, nickel, zinc, tin.	Arsenic dust in air from roasting arsenical ores.
Copper refined in the wet way.	Arsine.
Hydrogen for balloons, limelights, when made from iron or zinc and an acid.	Arsine.
Phosphoric acid.	Arsenic trioxide.
Sulphur and allied industries.	Arsenic dust, arsine.
Arsenic and arsenical preparations.	Arsenic dust in mines, charging and emptying retorts, handling products.
Galvanized iron, tinned iron.	Arsine.
Zinc chloride.	Arsine.
Coppers (ferrous sulphate).	Arsine.
Aniline dyes by the arsenical method.	Arsenic acid, arsenous acid in dust, in air or on hands.
Artificial flowers, leaves, etc.	Arsenical pigments or dyes by contact, or in dust in air.
Stuffed animals, birds, preparation of natural history specimens.	Arsenic trioxide, arsenical soap and fluids absorbed by hands or in dust.
Bird shot (arsenic used to harden the lead).	Arsenic dust.
Aniline from nitrobenzene.	Arsine.
Indigo blue.	Arsine.
Embalming fluids.	Arsenic trioxide, arsenites of sodium, potassium calcium.
Preservation of wood.	Arsenic dust.
Wall papers, colored papers.	Arsenical dyes and pigments in dust or by handling.

Channels of Introduction.—Accidental poisonings are the result of swallowing the poisonous material, breathing arsine or arsenical dust, or occasionally absorption through wounds or through the sound skin. But in criminal cases every conceivable channel has been used, the usual mode of introduction being in food or drink. A number of cases are recorded in which the poison has been administered to the victims by enemas or vaginal douches. The legend that Ladislas, King of Naples, met his death in 1414 by arsenic introduced into the vagina of his mistress by a jealous courtier, and that Calpurneus murdered his wives by digital introduction of arsenic into the vagina are probably not mere myth and fiction, for we find several modern imitators of Calpurneus. In one instance the arsenical material was introduced by placing the poison under the prepuce, and introducing it into the vagina in this manner, so as to avoid all danger of detection. In another instance three wives were successively murdered by placing in the vagina a mixture of flour and arsenic trioxide. Experiments on animals have shown, beyond the possibility of a doubt, that death may result from arsenical poisoning through such an introduction of the poison into the body. A few cases are found in which arsenical vapors have been employed with criminal intent, as for example the vaporization of arsenic trioxide and the roasting of arsenical pyrites in a room.

Fatal Dose.—Brouardel's investigations have shown that the toxicity of arsenic varies according to: (1) The method of administration; (2) the kind and age of animal; (3) the nature of the food material present in the alimentary canal. Owing to the fact that some persons have, to a certain degree, a natural or acquired resistance to arsenic it is difficult arbitrarily to set any definite figure as representing a fatal dose. Moreover, when the stomach contains a large amount of fatty material a huge dose can apparently be ingested without fatal results. It is to be said in this connection that a very large dose is seldom as dangerous as one consisting of close to what may be said to be the normal fatal dose, for the reason that vomiting is apt to be immediate and the poison is removed at once without having undergone resorption. For As_2O_3 the toxic dose for man can be set as lying between 5 mgm. and 50 mgm. (0.07–0.77 grain), and the fatal dose 100–300 mgm. (1.54–4.63 grains). For Paris green the doses are probably somewhat higher than twice these quantities. The above figures refer to per-os administration. When the poison comes in direct contact with the blood, as for example through wounds, the abraded skin, or the direct introduction into the body by some sharp instrument, it is about ten times as active. Rouyer has attempted to calculate the toxic and fatal doses on the basis of the amount of poison resorbed rather

than the total amount taken. According to his experiments and calculations 0.6 mgm. As_2O_3 resorbed per kilogram body weight will give rise to serious symptoms; 2.5 mgm. per kilogram may cause death in twenty-four to twenty-five hours, while 3 mgm. per kilogram will always cause death in about eight hours. It would seem that Rouyer's figures are probably too high, for they would require the resorption of about 200 mgm. to cause the death of a man of average weight. The actual dose to be ingested would therefore be considerably higher.

In the case of animals we find great variation in the intensity of the action of arsenical compounds, not only with respect to species, but also in different individuals of the same species. Von Gohier has seen a horse remain to all appearances in good health after a dose of 30 gm. of arsenic trioxide, while on the other hand 8 gm. has caused death. Not only do we have this variability of action on different individuals, but veterinarians are fairly well agreed that, particularly in the case of cattle and sheep, an animal may at one time stand a dose as high as 20-30 gm., while the same identical animal will suffer severe illness from 5 gm. at another time. The following table, while necessarily more or less arbitrary, can be taken as probably as nearly in accord with experimental data as is possible with our present knowledge.

	FATAL DOSE.	
	When taken internally.	When by wounds.
Horned cattle.....	10.0 to 30.0 gm.	2.0 gm.
Horses.....	10.0 to 25.0 gm.	2.0 gm.
Sheep, goats.....	5.0 to 15.0 gm.	.2 gm.
Swine.....	.5 to 1.0 gm.	.2 gm.
Dogs.....	.1 to .2 gm.	.02 gm.
Fowl.....	.1 to .15 gm.	.01 gm.
Pigeons.....	.05 to .1 gm.	.005 gm.

It will be seen from the above that sheep and goats are, per kilogram weight, remarkably resistant. A similar resistance is frequently met with in certain dogs.

Habitual Use, Tolerance, Arsenicophagia.—Aside from certain species of fungi and bacteria, arsenical compounds are toxic to all other forms of life. But by repeated small doses a certain immunity is at last acquired, after which enormous doses can be swallowed with impunity. This fact was known in most ancient times, for we are told that Mithridates (first century B.C.), who was well versed in the poison lore of his time, acquired immunity in this manner to protect himself against poisoners. By far the most striking cases of acquired tolerance are to be found among the mountaineers of Tyrol, Styria, Carinthia, the Punjab, and in some parts of the mountain ranges of South America. These mountaineers start taking arsenic, in the form of orpiment or the trioxide, from their youth; the men believing that it enables them to endure greater fatigue, wards off the mountain sickness and makes breathing easier; the women in order to improve their complexion, to acquire shining eyes, a rosy tint, and a well-rounded form. These arsenicophages seem to enjoy perfect health and reach an advanced old age. They exist, however, in a pseudo-normal state, for the suppression of the daily dose of arsenic leads to serious illness. The majority never reach a very high daily consumption of the drug, but instances are not lacking in which the amount taken daily reaches 300-400 mgm. We also have proof positive that certain individuals have taken this same amount at a single dose without suffering any inconvenience thereby. This tolerance and habit seem in many cases to be hereditary. A somewhat similar resistance is met with in patients who have been subjected to arsenical treatment with increasing dosage. After a time considerably over the maximum dose is tolerated. In Europe and in America certain waters are found containing arsenic. These waters have been long used by the inhabitants of the district, but no evil effects have been reported.

The administration of arsenic to horses by grooms in

increasing doses has been practised for many years, especially in England, the object being to improve the animal's coat, aid the assimilation of food, and to give them a plump, well-rounded appearance. The arsenic is either mixed with the food or is tied in a tiny piece of cloth and attached to the bit. This latter procedure results in the production of a slight salivation and the appearance of white foam about the mouth, the animal holding its head erect and champing at the bit, conditions which are supposed to indicate a spirited animal. Horses subjected for any length of time to this treatment require a continuance of the daily dose, without which they rapidly lose flesh and condition.

There is as yet no satisfactory explanation for the acquired tolerance of arsenic. The theory that there is an abnormal rate of elimination by the kidneys is not well established, and is insufficient to account for all the facts.

SYMPTOMS. ACTION.—With the possible exception of the gaseous compounds all other arsenical substances may be said to have a like action on man. No matter, therefore, in what form arsenic is administered the symptoms observed will not differ to any appreciable extent. These symptoms can be grouped under four different heads. Those typical: (1) Of a mineral acid—acidismus. (2) Of a mineral salt—metal toxicosis. (3) Of action on the nervous system: (a) splanchnic paralysis, resulting in hyperæmia of all abdominal organs; (b) neuritis. (3) Of inflammation of the intestinal tract and of fatty degeneration, especially of the heart. The result of the ingestion of the poison may lead to either acute or chronic poisoning. In acute poisoning it is possible to distinguish three forms: A gastro-enteric or ordinary form, paralysis arsenicalis, and asphyxia arsenicalis.

Acute Poisoning.—Ordinary Form. Soon after swallowing the poison the victim complains of a disagreeable metallic taste in the mouth, of an annoying burning, itching, or tickling dryness of the throat, there being usually frequent spitting and more or less salivation. This is generally, but not always, followed by pain in the upper part of the alimentary canal which gradually passes downward, increasing in severity. In most cases in from one to two hours, rarely later, after swallowing the poison, nausea, vomiting, and purging set in. In the event of Paris green being taken, vomiting sets in at an earlier stage than is the case with other arsenical compounds. The vomited matter may be streaked with blood, or green if copper compounds are present. In a short time the stools which were at first colored with bile, become frequent and rice-water-like. Usually there is tenesmus. The patient finds more or less difficulty in swallowing, suffers from dizziness, headache, pains in the limbs, a burning unquenchable thirst, and often a distressing hic-cough. The abdomen is distended and is painful on pressure, the secretion of urine is diminished, and there may even be anuria. The patient's voice becomes hoarse, features pale and haggard, eyes sunken, skin cold and dry. The pulse becomes slow and weak; respiration difficult and oppressed, and death usually takes place in fifteen to twenty-four hours, but often on the second day. The patient is ordinarily conscious to the last, but there may be coma, paralysis, or convulsions. If death does not occur before the second or third day, there is usually an apparent general improvement, save for the persistence of the dryness of the mouth and severe thirst. The temperature remains about normal or very little above. There is apt to be extensive erythema or an erysipelas or œdematous swelling which is most marked on the face and genitals, but there are patches more or less scattered over the body. There may be falling out of the hair. Blebs or pustules may appear on various parts of the body, or there may be circumscribed efflorescences. In many instances recovery is difficult and very protracted. Arsenical applications to the sensitive skin ordinarily give rise to severe dermatoses; as, for example, arsenical eczema of the legs and thighs from contact with trousers or stockings colored with arsenical aniline dyes. There may even be gangrene.

Arsenical paralysis is seen in both acute and chronic

poisoning, but an extensive paralysis is rare. Seisser in the famous Württemberg mass-poisoning observed only 1 case in 373. Alexander has collected the records of 55 cases of arsenical paralysis; of these 17 resulted from chronic arsenicism, while 38 were acute. In the great mass-poisoning in Great Britain in 1900, a very large proportion seem to have been troubled with paralytic symptoms. When arsenical paralysis results from acute poisoning it does not usually appear prior to the fourth day, or even the end of the first week. The normal termination of the seizure is the first half of the second week. The beginning of the trouble is marked by pain and paranæsthesia; soon there is numbness of the hands and feet, extending to the forearm and lower leg; very rarely is the paralysis of greater extent. Pain, which is seldom absent, may be very severe (anæsthesia dolorosa); it may be either constant or intermittent. The paranæsthesia has been variously designated by patients as a "sleepy," "furry," "itching," or "tingling" sensation. The hands and feet are cold, the tactile sense is disturbed as well as the temperature sense, cold water is mistaken for warm, while hot water is not recognized as such. As a rule loss of motility follows in a few days, but may also occur simultaneously with the paranæsthesia. In the majority of cases the patient cannot walk or stand for weeks, or even months, after the attack, but occasionally the effects soon disappear. The muscles first and chiefly affected are the extensors and abductors of the toes, later those of the fingers, and finally those of the lower and upper limbs. According to the investigations of Imbert-Gonebreyre the paralysis may be confined to the knees and elbows. Following the paralysis there is increasing muscular atrophy, which may reach an extraordinary degree of severity. Von Marik has described a case in which almost all the body muscles were affected.

Paralysis arsenicalis may be confused with tabes, alcohol neuritis, syringomyelitis, etc.

Asphyxia arsenicalis is a term given by several authorities to rare cases of exceptionally acute arsenic poisoning with unusually rapid death. In this form there is extraordinarily severe intestinal catarrh with vomiting, diarrhœa with rice-water stools, tenesmus, tonic convulsions first of the lower limbs, later of the upper limbs, cyanosis and death, with marked paralysis of the muscles of respiration in a few hours. This form of poisoning bears a striking resemblance to cholera asiatica of malignant type.

Chronic poisoning is seen most often in workmen in the metallurgical industries, in dye and paint works, among taxidermists, etc. A detailed list has already been given. Hill has also recorded a very unusual case, the alleged result of burning gas made from coal very high in arsenic.

According to Brouardel and Pouchet, who have made one of the most careful studies of arsenicism, there are four distinct phases in the progress of the disease. These phases correspond quite closely to the grouping given above under acute poisoning, but are more marked. The early stages of the disease can be characterized as protracted gastro-enteric catarrh. There are loss of appetite and vomiting of mucus and bile. Vomiting and pain may, however, be absent. The patient is apt to suffer from headache, faintness, irregularity of the bowels, depression, and loss of sleep. The breath is fetid, and the perspiration exhales an alliaceous odor like that of arsine. There is great emaciation. Fever and œdema may or may not appear. The urine is albuminous, contains hyaline cylinders, and substances reducing Fehling's solution. Sugar is rarely present. The urine contains arsenic, and on standing deposits magnesium-ammonium arsenate. A common accompanying symptom of much diagnostic value is obstinate conjunctivitis, together with redness and burning of the eyelids, and defective tear secretion. The throat and nasal passages are sometimes dry and irritated. The voice is hoarse. There may be slight cough, which, in cases arising from breathing arsenical dust, passes into more or less severe bronchitis. At other times the victims suffer from an influenza-like

snuffle and the nasal secretions are flecked with blood. Many cases of arsenicism have been diagnosed as "grippe," "cold in the head," etc. The skin is far more severely affected than in acute poisoning. There is generally urticaria or an erythematous eruption, or desquamation. Sometimes papules or vesicles form on the breast, back, and face, while later pustules may appear in the arm pits, upon the scrotum, or in the vulva. Frequently the face takes on a dusky tint, and there is marked pigmentation of most of the exposed parts and the pressure areas of the body, or this pigmentation is confined to the knees, about the neck, and to the region of the stomach. The victim appears to be dirty. So dirt-like is this pigmentation that patients upon their admission to hospitals have been given several successive baths. The hair first turns gray, then falls. There may be growths on the nails; the latter may even be shed. Hyperkeratosis of the hands and feet of short duration is seen in not a few cases. Following the typical symptoms of cachexia and muscular atrophy there is wasting away of the muscles, especially of the lower limbs, though the arms may also be affected and the hands become claw-like. Icterus is neither constant nor characteristic, yet is frequently observed. It never reaches the intensity met with in poisoning by phosphorus. True paralysis arsenicalis seems to be of less frequency in chronic poisoning than in acute; but if it does appear its effects are of greater duration, lasting even a life-time. There are often hemianæsthesia and hemiplegia. According to the reports of cases of poisoning from arsenical beer, published in the *Lancet* in 1900-02, it would appear that a large percentage of the victims suffered from more or less marked paralysis, as shown by difficulty in walking, numbness, pricking, tickling, etc., of the lower limbs from the knees down, and from the elbows down, often accompanied by exquisite pain.

Mackenzie has reported cases marked by paralysis of the vocal cords. Another peculiar form of paralysis has been studied by Charcot and Biët, and has received the designation anaphrodisia arsenicalis, because of the fact that the disease is characterized by a paralysis of the nerves of sexual sensation. Five typical cases are known. The physical diagnosis of chronic arsenical poisoning is very difficult. The most reliable method of reaching a decision consists in testing the urine for arsenic. This chemical diagnosis must never be omitted. The fatal period in chronic poisoning is too variable to permit of any statement.

Poisoning by arsenic may sometimes be confused with poisoning by phosphorus, antimony, ricinus, croton, abrus, robinia, podophyllum, etc.

Elimination of arsenic takes place chiefly by the kidneys; but there is reason to believe that in addition to the urine, the bile, milk, and perspiratory fluid play an important part, and that a certain portion of the poison is still further thrown out through the intestines. Arsenic can be detected in the urine in from two to eight hours after resorption, and is usually completely eliminated from the body, save from the bones, in from eight to twenty days. The normal period of elimination seems to be from twelve to fifteen days. This holds true only for acute poisoning, since in chronic poisoning, followed by recovery, the liver seems to retain arsenic for a long period; just how long is not known, but in animals it has been shown to be beyond forty days after the ingestion of arsenic ceased. Wood asserts that he has found arsenic eliminated eighty to ninety days after ingestion. On the other hand, Kunkle reports a case of poisoning by copper arsenite followed by death in seventeen hours, yet no arsenic could be detected in the liver, the stomach, or the intestines.

Saveri has shown that the arsenic eliminated by the urine is in the arsenous condition. Selmi has gone a step farther and has shown that part at least of the arsenic is eliminated in combination with organic matter as an arsenical organic compound, and that doubtless another portion of the arsenic is eliminated as arsine. The question of the elimination of arsenic through the milk is one

of very great importance. In the light of experimental evidence and of cases collected, it is now possible to assert positively that an infant nursing at the breast may die of arsenical poisoning when its mother is undergoing arsenical treatment, or has swallowed some arsenical compound yet not in sufficient amount to give rise to illness of the mother; or, in case of a toxic dose having been ingested, there may be death of the infant before the appearance of symptoms of poisoning in the mother.

For information as to the localization of arsenic and its distribution in the body after death, the reader is referred to Vol. VI., p. 722, of the REFERENCE HANDBOOK.

Post-mortem Appearances.—In acute poisoning the findings are but slightly characteristic. In rare cases negative results will be obtained, but only when death has been unusually rapid, as for example in cases of arsenical asphyxia. No matter through what channel the poison has been introduced, the mucosa of the stomach and intestines will generally be found to be swollen, covered with bloody foam, more or less uniformly red, intensely inflamed, or hemorrhagic. In some cases there is ulceration, even necrosis. A few cases of perforation are known. Corrosion may take place in a few hours (five or six), and after ten hours may be very severe; this may not be confined to the stomach alone, but may be seen in the intestines. The small intestine is commonly more or less filled with colorless, watery, offensive contents, while the large intestine contains fecal matter colored with bile. The liver, though apparently normal, shows on section marked fatty degeneration. Similar conditions obtain in the kidneys and heart. The blood shows no specially marked change, but its alkalinity is greatly decreased. In all but a few cases there is a remarkable preservation of the body with the internal organs fresh and of almost life-like consistence, or there may be mummification. Either of these conditions existing in an exhumed unembalmed body should lead to a strong presumption of death by arsenic, but the practitioner must never lose sight of the fact that preservation and mummification are far from being constant or peculiar to this poison. In deaths following chronic poisoning the findings are quite uncertain. The most constant are atrophy of the muscles, a dusky skin often marked with blackish patches, alopecia, gastro-adenitis, and hepatic, renal, and cardiac steatosis.

The *mechanism* or action of arsenic compounds can be briefly summed up as follows: (1) Local cauterization; (2) vaso-motor paralysis of splanchnics; (3) degeneration of albumin of the body and disturbance of metabolism; (4) disturbance of activity of the central nervous system and of the skin; (5) paralysis of the heart.

Following the paralysis of the peripheral extremities of the splanchnic nerves there results great hyperæmia of the abdominal organs, giving rise to an appearance of inflammation. This condition extending to the mucosa becomes severe gastro-enteritis, explaining why it is that these lesions are seen, no matter what may have been the mode of entry of the poison. The disturbance of the metabolism leads to fatty degeneration of most of the internal organs, and especially of the glands. When this steatosis affects the walls of the blood-vessels, multiple hemorrhage results. As an immediate consequence of fatty degeneration of the heart muscles the ganglia become affected and cardiac paralysis results. The severe cerebral disturbances sometimes seen can be ascribed in part to the sinking of the blood pressure, and in part to degeneration of the ganglionic cells of the brain.

Normal Arsenic.—The question as to whether arsenic is a normal constituent of the body has been the subject of several investigations within the last few years. The weight of evidence seems to support the theory of Armand Gautier, that arsenic is always to be found in the healthy body at least in the thyroid, where it plays an important part, and in the hair, nails, bones, and mammary glands, and that this normal arsenic is eliminated chiefly by the skin and the milk. Before this theory can be accepted as proved more research is needed.

ANTIDOTES. TREATMENT.—The most effective antidote with which we are now acquainted—freshly precipi-

tated ferric hydrate—was first proposed by Bunsen in 1834. It depends for its efficacy upon the fact that it unites with arsenous acid, arsenites, or arsenates to form insoluble compounds. With arsenous acid or arsenites a basic ferric arsenite results, mixed with a variable proportion of basic ferrous arsenite, while with arsenates a basic ferric arsenate is formed. The ferric hydrate must be freshly prepared, since it soon loses the power to unite to form an insoluble compound. The official method of preparation is as follows: To ammonia water (U. S. P.), 110 c.c., add water 250 c.c.; to solution ferric sulphate (U. S. P.), 100 c.c., add water 1,000 c.c. Pour with constant stirring the solution of ferric sulphate into the ammonia water, pour the mixture on a muslin filter, squeeze, and add to the precipitate sufficient water to make about 250 gm. Of this final preparation administer to an adult two to four tablespoonfuls every ten minutes. The dose for a child is one dessertspoonful every ten minutes. Hydrated magnesium oxide, proposed by Bussy in 1846, is also of much value. Like the iron antidote it must be freshly prepared. One part of freshly burnt magnesium oxide is suspended in twenty parts of water. Of this preparation four to six tablespoonfuls may be administered every fifteen minutes. As in the case of iron, insoluble basic arsenites and arsenates result. In Europe the two above antidotes are combined, as, for example. To Liquor ferri sulph. oxydat. (P. G.) 100 gm., add water, 250 gm. To water, 250 gm., add magnesia usta, 15 gm. Mix the two solutions, shake well, and throw upon muslin.

Both the iron and magnesium compounds must be removed from the stomach as soon as possible, since the insolubilized arsenic may be again resorbed through the solvent action of the fluids of the body. A recommendable procedure is to wash out the stomach with water holding magnesium oxide in suspension; then administer the antidote. After a few minutes induce vomiting, or use the stomach pump. Repeat this process several times. Demulcent drinks should be promptly given to retard resorption—milk, albumen in water, flour and water, etc. Following the antidote, the treatment must be symptomatic. It must never be forgotten that during convalescence the diet must be watched with great care, and only bland articles given.

In the absence of the above-mentioned antidotes, ferric hydrate, prepared in any way, can be given, or the following may be employed with more or less success: saccharate of iron, acetate of iron, citrate of iron, dialyzed iron, powdered or reduced iron, milk of lime, sulphur, sulphide of iron, etc. The administration of alkalies must be carefully avoided.

POISONING BY ARSINE is probably of greater frequency in the industries than is generally believed, though acute poisonings are quite rare. Arsine or arseniureted hydrogen is a heavy colorless gas of peculiar fetid odor. Its specific gravity is about 2.7. It is but slightly soluble in water, and burns with a characteristic bluish-white flame. The pure gas is a frightfully active poison, only a whiff or two causing death. Of some twenty cases of acute poisoning on record, practically all have been the result of chemical laboratory accidents, but subacute and chronic poisonings are frequent in the industries where small amounts of arsine are breathed in the air of ill-ventilated work-rooms. Although the odor of arsine is characteristic and very penetrating, the gas may be present in the air of a room in sufficient amount to lead eventually to poisoning, and still not be detected by the sense of smell, or at least not noticed. Poisoning occurs chiefly in the preparation of hydrogen and the manufacture of balloons or toy balloons; in the coloring or bronzing of brass and other alloys; in the desilvering of lead and subsequent treatment of the silver zinc with acids; in the galvanizing and tinning of sheet iron; in the reduction of nitrobenzene, etc., in the aniline industry; in the manufacture of many salts; in fact, in all industries or operations where hydrogen is given off in reactions between compounds containing arsenic as an impurity. Besides these sources there is the further possibility of

poisoning from wall papers in damp, ill-ventilated rooms through the formation of arsine by fungi and bacteria.

In strictly chronic poisoning the specific action of the poison manifests itself in anæmia or pernicious anæmia.

The effects of arsine on the system appear slowly. The victim shivers, complains of chills, and often of an indescribable feeling of sickness passing into great uneasiness and fear, resulting in exhaustion, weakness, and repeated fainting fits, during which the body is cyanotic, cold, and bathed in cold sweat. There is a blackness before the eyes and the pupils are dilated. There may or may not be nausea and vomiting. The pulse is somewhat accelerated but small and weak. Respiration is dyspnoic. The breath and mouth are fetid. After eight or ten hours, or even much later, the specific effects of the poison manifest themselves; the red blood corpuscles are destroyed and methæmoglobin is formed. All the urine passed is bloody, deep red, dark brown, or even black. There is sometimes anuria. Polycholia sets in and the skin becomes icteric or dark-colored. The stools are not watery as in arsenicism, but are colored dark with bile. The liver and spleen are swollen and painful on pressure. There are severe headache and a fear of death. Death occurs from œdema of the lungs or from paralysis of the heart. If death does not result the period of convalescence is generally very long. Spectroscopic examination of the blood for bands of methæmoglobin is of great value in diagnosis. These characteristic bands will also be noted after death, providing that an examination is promptly made.

The treatment of cases of arsine poisoning is difficult and unsatisfactory. Sodium bicarbonate should be administered to convert the methæmoglobin into alkaline methæmoglobin, which the body can readily change to oxyhæmoglobin. Transfusion of blood may often be imperative. The clogging of the canals of the kidneys has been successfully treated by injection of normal salt solution. The remaining treatment must be symptomatic. In the choice of stimulants to counteract the severe depression of the heart's action it should be remembered that alcohol is barred because of its action on the kidneys.

CLINICAL TESTS.—For the rapid detection of arsenic in the urine, vomited matter, stools, etc., where much organic matter is present, there is nothing superior to the Reinsch method, *i.e.*, acidification with pure HCl and boiling with a tiny strip of pure copper foil or gauze. The stained copper should then be tested by heating in a glass tube in contact with air and the crystalline sublimate of As_2O_3 examined with a hand lens or microscope. For inorganic material the modified Gutzeit test will be found to be rapid and reliable. The gases evolved by the action of sulphuric or hydrochloric acid on zinc in the presence of a solution of the material to be tested are passed through cotton moistened with lead acetate (to hold back any hydrogen sulphide), and are tested either with filter paper moistened with mercuric chloride or with a dry crystal of silver nitrate. In the presence of arsenic the mercuric chloride spot turns brick-red, orange, or brown; the silver nitrate crystal first canary or lemon-yellow, then black. *Emile Monnin Chamot.*

ARTERIOSCLEROSIS.—An exact definition of the term "arteriosclerosis" can not be given. The central idea is, of course, a hardening of the arteries. Our definition must be elastic enough to include the various stages of the changes in the arteries and should include the manifestations in the various organs that are affected secondarily by the disease. The complexity of the disease in its various manifestations is, then, an obstacle to an exact definition. The pathologists are not in entire agreement among themselves as to what anatomical changes are characteristic, as to whether the disease is of an inflammatory or a degenerative type, or as to whether the lesions are manifestations of a general or a local disease.

Alterations of Pressure in the Blood-vessels.—This con-

stitutes the most striking disorder of the general circulation, and upon a study of its causes, effects, and control will be built this entire consideration of the subject. Indeed, the whole mechanism of the circulation has to do with the maintenance of high pressure or low pressure in one part or another of the vascular system as may be demanded. The maintenance of the circulation is not a question of the degree of tension in any part of the circulatory system, but of a proper relation in tension between pressure in the arteries, where the blood is stored, and the points at which it is needed. It is usual, however, to study the question from the standpoint of the arteries. In most cases it is only late in circulatory disease that venous pressure becomes of importance. The freedom of passage between the arteries and veins through the arterioles and capillaries is of extreme importance.

The effect of muscular exercise on blood pressure is at first to raise arterial pressure, but finally, after the exercise has been continued for some time, the pressure falls again to normal. The same is true in regard to the effect of mental effort. During the existence of this increase of arterial pressure due to exercise, there is a large amount of blood in the arteries. This is obtained from the large veins in the abdomen, which act as a reservoir from which, in health, blood can be drawn to flush any part of the arterial system. This tide of blood between the digestive organs and the systemic area is illustrated in many ways. Thus, the coldness after eating indicates that the tide has set toward the digestive organs. The indigestion following exercise after eating, and even more markedly the indigestion following strong emotion after a meal, shows that the tide has set the other way. The lethargy and mental inactivity of those who habitually overeat, and the tendency to indigestion of mental workers, indicate the same thing. The relation between the circulation in the abdomen and the circulation in the brain is an intimate one. The proverbially good mental condition in patients suffering from acute peritonitis may very well be due to the spasm of all the abdominal muscles that prevents the accumulation of large quantities of blood in this part of the body.

The impression of the circulation obtained by one's early study of physiology is erroneous. It resembles too closely the idea of a series of closed pipes, as in the plumbing of a house, the water entering at a large pipe, going through a system of smaller pipes, and, after having been used in certain fairly definite receptacles, being collected by a similar set of pipes which convey it to a common outlet. The facts, however, are very different in the human body. The arterial system is really a reservoir of blood in which the area of a cross-section of the combined vessels very rapidly increases from the heart outward. In this series of passages the blood is contained and held under pressure by a muscular envelope. From this reservoir the blood escapes for use, through the arterioles and capillaries, and the office of the heart is to pump into this reservoir sufficient blood to maintain the pressure depleted by the blood used by the capillaries. This naturally creates a flow of blood from the heart toward the periphery, but the immediate use of the heart is to maintain this arterial pressure. This is well shown by the fact that the actual amount of blood propelled by the heart varies greatly, according to the demand for fresh blood on the part of the body. During exercise, when the peripheral vessels are open, and there is a drain on the arterial system, the heart works harder to supply the deficiency. Thus the arrangement and movement of blood in the body are seen to be more like a system of irrigation than of circulation, there being a reservoir with numerous branches from which the irrigating fluid is distributed and a system of conduits by which it is collected, to be again transferred to the storage place.

The idea of the office of the veins as a storehouse of blood is a very old one, and one which has had much influence upon therapeutics. The consideration of the arterial system as a similar reservoir in which suitable pressure is maintained by the muscular elements which

go to make it up, seems to have been overlooked. The truth of the statement that the arteries form a reservoir rather than mere conduits is shown by the fact that arterial pressure is practically uniform throughout the arterial system. This means that the blood moves with the utmost freedom throughout the arteries, and that its movement is controlled, not by pressure from behind, but by the escape from in front.

The arterial system is thus like a reservoir analogous to the tubular boiler of some types of engines. It is a hollow ramifying organ containing a vital fluid, the capillaries being the ducts. Whenever there is a demand for this vital fluid in any part of the system, the muscular covering of the organ contracts, the arterioles which lead to the proper capillaries dilate, and the demand is supplied. The demand upon this organ for the vital fluid is so great that a special mechanism, represented by the heart, conducts the vital fluid from the places where it is manufactured, and the lungs where it is purified, to the high-pressure receptacle from which it is used. This conception of the arterial system as a high-pressure receptacle for the blood is well borne out by a study of the evolution of the circulation in the lower forms of life, where there are first found small interstices in the tissues through which the blood ebbs and flows in an irregular manner. As we ascend the scale the blood is found in more definite receptacles, until finally we reach the complex arrangement found in man.

The so-called circulation of the blood was discovered very late in the history of man, and students have become so fascinated with the mechanical beauty of the whole arrangement that they have allowed the mechanical idea to outweigh the realization of a living organism. It is the old truth of the pendulum which has swung too far when once started by Harvey. We need to return a little to the earlier conception, which considered more the function of the blood in particular parts of the body than its circulation. In all studies of blood pressure it must be remembered that the blood is subject to the laws of hydrostatics and that the force of gravity must be discounted.

Anæmia and Congestion.—In the study of the circulation in relation to disease, the two departures from normal that are most striking are anæmia and congestion. But a moment's thought will show that these are not necessarily of as much importance as would appear. The other element, that is not so easily appreciable in the course of examination and upon which depends the efficiency of the blood supply, has very little to do with anæmia or congestion. Anæmia means that there is but little blood in the part under consideration, and congestion means that there is a considerable accumulation of blood in the vessels of the part. These two things are very striking symptoms of disease; and yet every clinical observer must have noticed that they are not reliable indications of disease.

The third element of local circulation in disease is the amount of new blood supply to the part which is the determining element in degeneration or repair. There may be apparent anæmia, and yet what blood there is in the part may be constantly changed, and nutrition will not suffer. There may be marked congestion of the part, and yet the amount of fresh blood supplied and of impure blood removed may be sufficient.

This element is a very hard one to determine, even experimentally. The pulse itself does not indicate any transition of blood through the radial artery, because it persists, even when the artery is obstructed by pressure beyond where it is palpated and when no blood can pass. So, in a sufficient blood supply, or in an excess of blood supply, it is the amount of blood in circulation that is to be considered, and not the amount that is stored up in the part. In congestion without circulation, we find destruction of tissue, as in varicose ulcers of the leg. In congestion with circulation, we often find hypertrophy, as witness the clubbed fingers in chronic cardiopathy. In anæmia without circulation, we again find that the nutrition suffers; but in anæmia with circulation, there

may be no disturbance of nutrition. In other words, the circulation of the blood may be compared to the circulation of the money in a bank. So long as the intake and outgo are active, the bank is going on all right, whether there is a large or a small amount stored up in its vaults. Of course, in case of emergency, it makes a very great difference whether there is an accumulation or not. But under ordinary conditions, the outward signs of prosperity depend upon the in-go and out-take and not upon large or small accumulation. So, the importance of circulation is a question of movement of the blood, more than it is a question of particular location of that portion that is not in active circulation. Ordinarily, the part of the blood not in active circulation is found in the large veins of the abdomen, but it might just as well be in any other part of the venous system.

Estimation of Blood Pressure.—The estimation of the condition of the circulation usually represented by "feeling the pulse" stands for a very important procedure in the routine of the practice of medicine and is the one element of a physical examination that is probably never neglected. The tactile estimation of relative blood-pressure, as determined by the experienced touch and checked by clinical symptoms, is often correct, and there is a possibility that some of this skill in pulse-reading may be lost if instrumental observation takes the place of direct examination, just as we have lost skill in measuring fever. However, the benefit following the introduction of instruments of precision far outbalances the resulting loss of skill. It is undoubtedly true that the systematic instrumental measurement of blood-pressure by various instruments has led to important clinical results.

As remarked a moment ago, it is the difference in pressure between the place where the blood is stored and the place where it is required, together with the element of resistance in the intervening blood-vessels, that determines the competency of the circulation. The instruments and skill for the quantitative measurement of blood-pressure, although brought to a high degree of perfection, are still not in the possession of the majority of practitioners. Our space here will not allow anything like a detailed description of the development of these various instruments. It will suffice for our purpose here merely to refer to such instruments as that of Professor von Brasch, of Vienna, who in 1876 invented what may justly be considered the first practical sphygmomanometer; his own and Potain's improvement a little later; Marey's instrument, with Hurthle's elaboration for measuring diastolic pressure; Mosso's complicated but highly efficient apparatus for the laboratory, and Hill and Burnard's "vest-pocket" instrument, whose chief merit is its compactness. But the very number of this class of instruments invented within the last two decades shows the importance of the subject of accurate blood-pressure measurement. And this same prolificness insured such searching criticism of defects and struggle to overcome them that the perfected instruments of Riva-Rocci, Cook, Stanton, and others may now fairly be considered practically to be instruments of precision.

In this country, Dr. Theodore C. Janeway has produced a sphygmomanometer of such compactness, accuracy, and simplicity that a brief description of it is given here. It is made by Chas. E. Dressler & Co. of New York. The author's own description of his instrument is as follows ("The Clinical Study of Blood-pressure"): "The only original feature is the folding U-tube manometer (A). This is shown in the plate in position for use. For carrying, the upper joint of the manometer tube is removed and slipped through the rings to the right. The open end of the U is then closed by a small cork (F); and other end is closed automatically when the case is shut, by a block which compresses the rubber joint (G). The scale is slid down, the Politzer bag (C) removed from the stopcock (E), which contains a needle valve for slow release of pressure. This stopcock is allowed to slip under a spring (H) as the case

closes. The lid, to the under side of which the manometer is fastened, is then closed by dropping the catches which hold it behind and folding down the hinge at the left, the lower end of the lid sliding back in a groove. The whole when closed measures $10\frac{1}{2} \times 4\frac{3}{8} \times 1\frac{7}{8}$ inches and, with the armlet and inflator, weighs $2\frac{1}{2}$ pounds. The manometer tube has a calibre of 3 mm. and all the connections are of heavy-pressure tubing. The armlet (B) is a

and to this a blue tube and a blue bag, measuring to the center of the bag 136 cm. Connected to the blue bag is a cord passing through a pulley of special construction. This pulley is so constructed that it can be easily hung at a height by means of a cane or similar implement. I have also devised a special scale which is attached to the bag at the level of its contents and is used to ascertain the blood-pressure in terms of millimetres of mercury. The instrument can be rolled up and carried in the pocket, and is used as follows:

"The tube is separated at one of the connections between the different colored tubes, and the air is drawn out of the two bags by suction, by placing the ends of the tubes one at a time in the mouth. The bags are now placed on the floor, and the ends of the tubes plunged in a basin of water and about 14 ounces allowed to siphon into

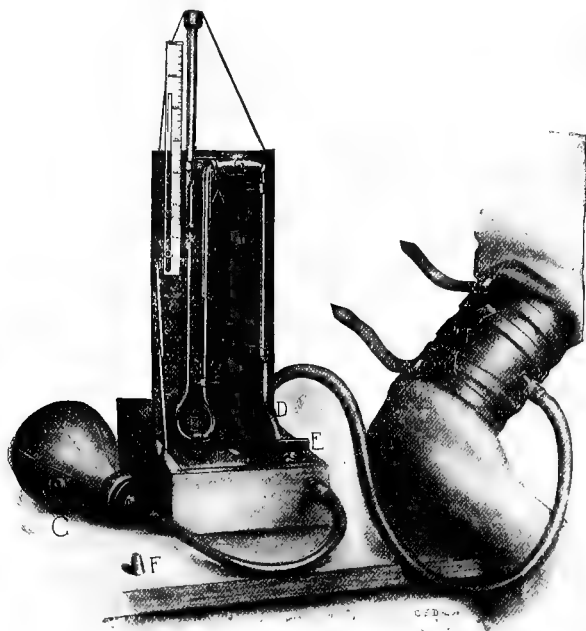


FIG. 5062.—Janeway's Sphygmomanometer.

hollow rubber bag, 12 cm. wide by 18 cm. long with an outer leather cuff 15×33 cm., fastened, as the illustration shows, by two straps with friction buckles, which will catch at any point. The buckle employed makes adjustment to different arms much easier than the ordinary tongue buckle. Experience with the latter has taught me that one hole may be too tight and the next too loose. For the inflating mechanism I have followed Erlanger in adopting the ordinary Politzer bag, though I find one with the valve necessary to fill the 12-cm. armlet. The needle valve is manipulated with ease, even by a novice, and allows a very gradual or a sudden lowering of pressure equally well. As accurate manometer tubes cannot be made in this country, each scale is graduated empirically, the reading at each point being the exact difference between the level of the two columns of mercury. The instruments are therefore accurate. The procedure in general is the same as with Stanton's instrument."

Dr. Louis Faugères Bishop's simplified blood-pressure detector is particularly useful for the detection of high pressure and low pressure cases in general practice and life-insurance examinations. The inventor's own description of his instrument on its presentation to the New York Medical Society (1908) was as follows:

"The simplified instrument consists essentially of a red armlet 15 cm. wide and 40 cm. long, made of strong material. This armlet or cuff differs from the Riva-Rocci armlet in its greater width and in the fact that the rubber bag occupies only part instead of the whole circumference of the arm. The advantage of this latter arrangement is that the rubber bag when expanded compresses the artery against the bone, rather than surrounds the whole arm which proved to be painful. Connected with the cuff is a red rubber tube 203 cm. long. To this is connected a white tube 60 cm. long,



FIG. 5063.—Sphygmomanometer (Author's Model, as made by E. B. Meyrowitz, New York).

the bags. The ends of the tube are rejoined under water so that no air can enter. The red cuff is now lifted up so that the water runs into the blue bag which is left on the floor. Then the armlet is placed around the arm of the patient in such a manner that the part containing the bag comes on the inside of the arm. The pulley with the cord to it is now attached high up to a picture moulding or some other convenient object, and

the bag is hoisted slowly until the pressure of water that has flowed back to the cuff has compressed the brachial artery and obliterated the pulse at the wrist. To find the exact point at which this takes place it is better to lower the bag until the pulse is distinctly felt again, and then raise it two inches at a time counting ten beats of the pulse each time until the pulse disappears. If at this point the white tube be opposite the level of the patient's heart, or the level of the cuff, which is practically the same, having the patient in a sitting position, the patient's blood-pressure is within normal limits. If the blue tube is opposite this level, the patient has a subnormal blood-pressure; if the red tube, the patient has an increased blood-pressure. In order to measure the blood-pressure in terms of millimetres of mercury, my special scale is attached to the blue bag at the level of the water in it, when the apparatus is in operation, and the figure on the scale at the level of the heart when the pulse disappears indicates the blood-pressure in millimetres of mercury."

I have tested this apparatus with all kinds of cases and compared them with the standard instruments, and have found that its readings are correct. I find that a closer reading is often possible with this instrument than with the other instruments on account of the absence of fluctuation and greater length of the scale. This is especially true in low-pressure and very high-pressure cases. The instrument is particularly convenient for detecting cases that fall into my classification of blood-pressure cases, into primary low-pressure cases, high-pressure cases, and secondary low-pressure cases. On account of the great elevation of the pulley that is necessary it is not convenient for very high-pressure cases. This is simply overcome by using the instrument where there is a stairway or in a high-ceilinged apartment.

Etiology.—The causes of arteriosclerosis, using the term in the broader sense, founded upon advanced knowledge, may be divided into two classes, namely, those having their origin in toxic influences, and those having their origin in the progressive changes to which all beings are subject in the crises of growth, maturity, and afterward.

Arteriosclerosis resulting from nervous causes comes about through vascular strain from the maintenance of an abnormal blood-pressure produced by these nervous influences. To appreciate how this comes about, it is necessary to realize that there is a close analogy between the arterial system and the heart. The heart has its myocardium and the arteries their "myarterium." Thus, in the smaller arteries, there is a system of muscles and nerves capable, not only of causing contraction of the blood-vessels, but, according to the views of many physiologists, capable of producing an active diastole. This is also borne out by the teaching of Evolution, for we find, as we ascend the animal scale from the lower to the higher forms, that the circulatory tube becomes gradually differentiated, and it is only in the higher animals that we find the part of the tube represented by the heart so completely different from that represented by the arteries and veins. The nervous system acts upon the heart in what is usually spoken of as a very complicated manner, but only to regulate its activity as an organ that does one thing, namely, propel blood. The nervous system acts on the blood-vessels as organs which have to do with many different activities in the body, because every functional action influences a modification of blood-supply. Not only does the nervous system preside over the blood-supply to each particular part of the body at all times, but it also concerns itself with an adequate blood-pressure in the arteries.

Muscular overexertion is not a cause of peripheral arterial disease, though it does frequently cause disease of the aorta. It is, nevertheless, a fact that degenerative changes, consisting of calcareous incrustations, are found at an early age and more frequently among those who are engaged in occupations that demand great muscular effort, either all the time or at intervals; the same

changes are found in old people, as a simple result of age. These changes ordinarily give no symptoms, although, in case of the involvement of parts of the aorta close to the aortic valves or an extension to the arteries of the heart, the results are serious.

Goit is actually a potent cause of disease of the blood-vessels. The process in respect to the blood-vessels is probably much the same as that with regard to the joints; that is, an actual deposit of urate of sodium. Malaria, in its more severe forms, lead-poisoning, and severe infectious diseases may result in chronic arterial disease. The involvement of the aorta is ordinarily without symptoms, except when it goes on to the production of valvular disease of the heart and aneurism, which are not pertinent to the subject in hand. But there is an occasional exception, when aortic disease does give very distressing symptoms. I have observed the case of a gentleman, aged seventy-four, in whom the only symptom of any circulatory trouble was pain over the upper part of the breast bone when he attempted the slightest exertion. This has continued for years without the development of any sign of involvement of the aortic valves or symptoms of aneurism. The patient was instructed by me to take a small dose of nitroglycerin whenever he wished to exert himself, and, to the satisfaction of both of us, he then found he was able to exercise without pain.

Acute inflammation of the general arterial system is apparently very rare, or at least not recognized, although we have reason to believe, from studies of a number of recent writers, that the inflammatory processes set up during typhoid fever, scarlet fever, and diphtheria may lead later to fibrous changes. Syphilis is, of course, one of the most important single causes, but as this subject is treated fully in another part of this work, I will not dwell upon it here.

Symptomatology.—The symptoms of angiosclerosis, or, as we prefer to call it here, disorders of blood-pressure, divide themselves into subjective and objective groups.

The subjective symptoms depend upon the influence of circulation upon the sensory nervous system, and upon the appreciation by the individual of the local changes in the blood supply. Among the organs of the circulation are the brain and the kidneys. The brain is a highly sensitive organ, the most striking function of which is consciousness. The kidneys are insensitive organs. The brain is the most prominent organ of conscious circulatory symptoms, and the kidneys the most prominent organs of those symptoms of circulatory disease that develop gradually and insidiously. Changes in the peripheral circulation often go on simultaneously, producing evidently conscious symptoms, referred to the brain, which lead the physician to seek evidence of disease in the kidneys. From what was said, in the section on Etiology, of the nervous control of the circulation, it may be inferred that the most striking changes in the blood-supply are often found in nervous disease. In hysteria, neurasthenia, and other so-called functional nervous diseases, the vasomotor system becomes disturbed, so as to lead to the most erratic distribution of the blood. In true insanity of maniacal type, high blood-pressure is very common; and in depressed types, poor circulation, with cyanosis of the extremities, is most characteristic. From all this, it may be inferred that the symptomatology of disorders of the blood-vessels needs to be analyzed to separate the signs of important organic conditions from those that are not essentially due to disease of the blood-vessels, but are the temporary expression in the circulation of other conditions. In deciding this, the measurement of blood-pressure in the arteries is of the greatest importance, because the persistent rise of blood-pressure is an indication of circulatory disease, present or to be developed.

The direct examination of the radial artery for the detection of disease of the vessel itself is the first step in diagnosis of arterial sclerosis. Palpation of the radial artery, as represented by feeling the pulse, is the one element of physical examination that is never neglected

by any physician in any case of illness. Hence, it represents an unusual degree of experience. Arteriosclerosis is often detectable by the examination of the pulse, or rather of the radial artery and its pulsations. The artery is to be examined with the tips of all the fingers; first studying the pulse-wave, then the amount of pressure necessary to check these pulse-waves. Then the attention must be turned to the artery itself, which must be examined for patches of atheroma; not because atheroma and arteriosclerosis are the same condition, but because atheroma is very apt to be present in arteriosclerosis.

Diagnosis.—The diagnosis of circulatory disease depends first upon the recognition of disorders of the blood-vessels, and then upon the decision of the question whether these symptoms are merely due to the natural disturbance of the circulation incident to some other disease, or whether the condition is essentially a disorder of the circulation itself. But some other disease may originally cause the circulatory trouble, and the latter may persist after the other disease has come to an end, or outbalance it in importance.

When disease of the blood-vessels is suspected, the symptoms to be elicited in the interrogation of the patient are first those that the patient connects with circulatory disease and those that pertain to our own knowledge of the effects of disturbed blood-supply. The ordinary symptoms of vasomotor disturbance are chiefly observed in the skin. Dilatation of the blood-vessels is accompanied by sensations of heat, throbbing, and perhaps sweating. This vasomotor paralysis will be found most commonly with nervous symptoms, but frequently occurs as an independent affection. Or, on the other hand, in a case of vasomotor spasm, there are striking pallor and coolness of the skin, with a feeling of itching and often great discomfort. This is most frequently observed in the hands. Sometimes the patient will be conscious of heat and redness of one part of the body, while another part is cold and pale. Vasomotor disturbance may be so great as to give rise to local swelling, due to the effusion of serum, or even to gangrene due to vasomotor spasm.

The symptoms of circulatory failure are not alone dyspnoea, oedema, and visible congestion or anæmia, though these are the cardinal indications. There are certain symptoms of obscure origin traceable to circulatory disease, which are overcome only when that is given proper attention.

In elderly people, one of the most frequent and troublesome of symptoms is that of head noises. I have under observation at the present time no less than four patients who have suffered over long periods of time from noises referred to the ear, which they described as puffing or blowing sounds, and which have been extremely annoying. These patients had all been systematically and heroically treated for ear disease without benefit; but when the circulation was properly controlled, the noises became so slight as not to be complained of, and a good deal of the time not to be noticed. These patients are usually found in the group of commencing secondary low arterial tension. The explanation of these sounds would seem to be the circulation of blood through badly filled blood-vessels in the neighborhood of the organ of hearing. There is no class of cases that has given greater satisfaction, because it is possible to relieve the condition that causes so much suffering, particularly at night.

Another obscure manifestation of circulatory disorder is the simulation of slight attacks of paralysis. These are often overlooked unless they are watched for. They consist of a temporary slight loss of power of a transient nature, on one or the other side of the body. The patient usually describes the attack as a "clumsiness" of a leg or an arm. If on the right side of the body, there is sometimes a slight loss of power of speech, in that certain words are missing. The patient usually considers this a temporary failure of memory. These manifestations are often the same as those which indicate

more serious disease of the brain with impending thrombosis. However, in many cases, attention to the general circulation will entirely remove the symptoms, so that it is hard to believe that the condition was purely local in origin.

There is a class of obscure symptoms of circulatory disorder which consists of pain in various parts of the body. How much of this is purely circulatory and how much of it belongs to the gouty, rheumatic, and nutritional disorders that are common in the same class of patients, is often hard to determine. It is suggestive that these painful conditions arise at times of circulatory debility and improve when the circulatory disease is in abeyance. Attacks of sciatica of a persistent and troublesome nature are particularly apt to occur in patients commencing to suffer from secondary low arterial tension.

There is a really pitiable class of patients who may be mentioned here, though perhaps not quite logically. These are persons who have developed a very painful and chronic neuritis subsequent to attacks of extreme circulatory oedema of the lower extremities. It may be only a coincidence, but this has been among the most difficult conditions to relieve of all that have come under observation in connection with the treatment of circulatory disease.

The obscure symptoms of circulatory disease would not be complete without a consideration of those that may happen during the stage of high arterial tension. Nosebleed of a troublesome character is a frequent occurrence; and in cases in which one is puzzled to decide between primary and secondary low arterial tension the history of a period during which nosebleed was very troublesome may be of help. It is surprising how often this history is elicited from patients who come for the first time in the stage of broken compensation.

The number of conditions due to congestion secondary to general circulatory disease that are mistaken for diseases of local origin is very great. The most striking of these is, perhaps, congestion of the liver. This develops gradually, the blood collecting in the liver and giving rise to functional derangements of this organ and of the other organs of digestion. The liver is enlarged and tender on pressure, and the condition is often accompanied by very marked disorder of the stomach, on account of which it is frequently mistaken for primary gastric disease. That this is not the case is proven by the fact that the condition is relieved only when the circulation is strengthened.

The circulatory disorder may also be shown in its pulmonary effects. There is persistent congestion of the lungs, often with a tendency to the accumulation of serum in one or both pleural cavities. These patients may often have a fairly good systemic circulation and very obscure indications of cardiac disease. The interference is apparently with the function of the right side of the heart. Two patients of this character were watched over a long period of time, while the pulmonary congestion, involving repeated attacks of bronchitis and slight oedema, rendered them incapable of work. The circulatory disorder is masked because the symptoms are so much more accentuated in the thoracic organs than elsewhere.

Circulatory disorder may also show itself in its effect upon the function of the brain by attacks of acute mania, or more often by the development of a chronic mania. Changes in the arteries in elderly people are apt to be characterized by changes in disposition, by affections of the memory, and by impairment of judgment. The circulatory derangement may be shown by so striking a manifestation as general convulsions. These patients are often supposed to be suffering from idiopathic epilepsy. However, the attacks are so promptly relieved by appropriate treatment directed to the circulation, which would have no effect whatever in epilepsy, that this may be eliminated from the diagnosis. Of course, there are relatively rare cases in which real epilepsy begins late in life.

A group of symptoms on the border line between neurotic and circulatory disturbances forms in its sum total a large proportion of the sufferings of humanity. Abnormal sensations in the extremities, numbness and tingling of the hands and feet, a feeling of formication extending up the legs and thighs, abnormal coldness of the hands and feet, cramps in the muscles of the legs occurring at night, and the tendency of the extremities to "go to sleep" as it is called—all these things may be pure neuroses, but often enough there is a circulatory element in their causation. As was suggested in a preceding paragraph, we may again remark that the therapeutic test will decide how much of this is due to disorder of the circulation. Many times the symptoms disappear when the circulation is properly regulated. A few doses of nitroglycerin have stopped all complaint of cold extremities in many patients of this type. The possible severity of pain due to interference with the circulation is well shown in cases of embolism of the extremities in the course of circulatory disease. No one who has observed this accident will doubt that pain of the severest type may be due to interference with the circulation.

HIGH-TENSION AND LOW-TENSION CASES.—There are two great groups of high-tension and low-tension cases and a third group of secondary low tension following high tension.

Primary Low-pressure Cases.—Disorders of the general circulation are generally first recognized when some particular portion of the body becomes the seat of a marked congestion or anæmia. Then two conditions often produce symptoms that are strikingly similar. Delirium may be the result of congestion of the brain, but it may likewise result from anæmia. Dyspnoea may be an accompaniment of congestion of the lungs, but a deficient blood-supply is its most common cause. Acute congestion of the kidneys causes suppression of urine, while diminished blood-supply causes deficiency of secretion.

The effect upon an organ is a matter of the proper supply of fresh blood, not merely of a greater or lesser amount of blood in the vessels of the organ. This explains beautifully the effect of local therapeutics, such as the removal of a small quantity of blood, or the institution of some form of counter-irritation, the result of which is to start up a stagnant local circulation. There is, however, little gain from the treatment of local congestion or anæmia without attention to the general circulation in cases where the cause is general. Hence the extreme importance of recognizing which cases are of purely local origin and which have their origin from the general circulation.

During the acute stage of valvular disease, in the large majority of cases, circulatory failure does not become a matter of special anxiety. Low arterial tension usually shows itself when the patient resumes his ordinary occupation. The symptoms are practically the same for all forms of valvular lesions, although different in degree. The important question is whether the defect has been properly compensated, and whether this compensation can be maintained. In general, however, it may be considered that in aortic disease the defective circulation is more strikingly due to an insufficient supply of blood in the arteries, and in mitral disease to an increased pressure in the veins, both resulting in a diminution of the difference in pressure in the arteries and veins, upon which the proper passage of the blood through the tissues depends.

The belief, so firmly held by many, that cardiac disease is usually confined to the left side of the heart is not borne out in practice. The most serious and fatal disorders involve the right side of the heart. It is true that inflammation and distortion of the valves are almost entirely confined to the left side of the heart, but it is likewise true that both sides suffer equally in the incompetencies of the valves that come from strain or weakness of the heart muscle, as seen in very many cases of disorder of the circulation. The left side of the heart can be

markedly deficient in mechanical detail or physical structure and the patient may get along fairly well until dilatation involving the right side of the heart takes place with tricuspid regurgitation and its resulting venous engorgement.

Low arterial pressure is to be regarded as pathological only when it is so little above venous pressure that the tissues and organs are not properly supplied with blood. There are instances in which the heart is perfectly able and willing to produce more arterial pressure, but the peripheral circulation is so relaxed that it is not needed. We get dangerous low-pressure cases when the pressure-producing mechanism has failed. These are primary when there has not been a previous overdemand for pressure. Low blood-pressure due to general prostration is not to be regarded as a disorder of the circulation except in so far as the circulation fails to respond to demands made upon it. Thus in shock it is the nervous system that is at fault, not the circulatory apparatus.

The indications for treatment in disorder of the circulation characterized by deficiency in pressure in the blood-vessels, which is primary in that it has not been preceded by high arterial tension, are simple, though the elaboration of the management of each case will tax the judgment and ingenuity of the physician. When there is no defect in the valves and no tendency to obstruction in the arteries the condition is usually a weakness of the heart, and much may be accomplished by iron, arsenic, and hypernutrition, by increasing the number of meals, and by outdoor exercise.

In the early days of a newly acquired valvular lesion, prolonged rest in bed with the very gradual resumption of a more active life will enable both the heart and the body in general to adapt themselves to the new conditions. Of necessity, there must be a compensatory hypertrophy, but it is not to the advantage of the patient that the hypertrophy be excessive, hence the desirability of such gradual resumption of active work. Until subjective symptoms and objective signs of defective circulation have disappeared, the patient must be restricted to a very quiet existence. The use of drugs at this time is usually inadvisable, yet in cases of long-delayed compensation digitalis may be used.

When compensation is established and proper pressure in the arteries maintained, these cases may still be classed in the category of low arterial tension because of their tendency to this condition, just as we consider cases of Bright's disease as being high-pressure cases, even when the condition is not actually present at the time.

During the stage of compensation, which may be of long duration, the patient should lead a well-regulated existence—physical overexertion, mental overanxiety, and dissipation of all kinds must be avoided. The occasional use, during the stage of compensation, of the iodide of sodium as a means of preventing degeneration of the hypertrophied heart is a useful procedure even when no other drug therapy seems advisable.

In the progress of cardiac disease there are many elements that are not unlike the advance of tuberculosis. The term "cardiac cachexia" has been applied to a form of this condition accompanied by congestion, but it might well be extended to include the deterioration of fibre which leads to failure of the circulatory apparatus. In tuberculosis, the connection between the cachexia and the disease is so evident that its hygienic management needs no advocate. It is equally true that the progress of circulatory disturbances is often dependent upon nutritional causes, and that the hygiene of tuberculosis in its demand for fresh air is equally important to the cardiac patient. The vitalizing effect of fresh air in these cases will more than counterbalance the dangers of catching cold, although care is necessary when inflammation or congestion of the kidneys is present. The patient can be trained to sleep with open windows.

Low pressure due to degeneration of the heart muscle which has not been preceded by hypertrophy is not at all common except in connection with acute or chronic general disease. But little is accomplished by measures

directly influencing the circulation. The same is true of the heart overloaded with fat. Treatment must be hygienic, though the defective heart muscle demands precautions.

High-pressure Cases.—By high-pressure cases are meant those circulatory disorders which are characterized by undue resistance in the circulatory path of the blood. It is not necessary, for cases to be classed in this category, that actual high-pressure should always be present in the blood-vessels. High-pressure cases comprise all instances in which degenerative disease of the blood-vessels or kidneys, brain tension, or toxæmia causing disordered action of the same and resulting in high arterial tension, precedes or goes hand-in-hand with the development of cardiac disease.

Low-pressure cases occasionally become high-pressure cases, as when valvular disease of the heart causes secondary Bright's disease.

The management of high-pressure cases, which include a large proportion of the slowly developed diseases incident to the overwork and luxury of modern times, is relatively more important than that of the low-pressure cases. It is particularly important to detect the earliest development of a tendency to high arterial tension, because at this time it is more amenable to treatment.

As implied above, in this class of cases the heart, blood-vessels, and kidneys go hand-in-hand, and serious disease of one is not found without involvement of the others. Hence the term "chronic Bright's disease" is frequently used in speaking of these cases. But chronic Bright's disease is not essentially a disease of the kidneys, although in the final catastrophe these organs are often chiefly at fault. Primarily, it is a disease of the circulation in which the brain and kidneys, acting as it were as end-organs, first manifest symptoms.

A case which had been under observation for five years ended fatally by the involvement of the circulation of the brain, producing progressive stupor, and finally coma, paralysis, and death. The kidneys at the time were apparently in good enough condition to have functioned fairly well for a much longer time. In this case, the greatest care had been exercised in protecting the kidneys by diet, an even temperature, and every other possible means, thus allowing the arterial disease an opportunity for its complete development. The same case, if less carefully guarded, would have progressed, by repeated attacks of uræmia, to a death by the development of anasarca and exhaustion. We have, then, the paradox that a person may die from Bright's disease with fairly good kidneys.

This point is important in considering the early symptoms in high-pressure cases. The kidneys are insensitive organs, rarely giving rise to pain, intermittent in their manifestations, and entirely removed from direct observation; for this reason disorder of the kidneys may reach a grave stage before it becomes a matter of consciousness. On the other hand, the brain, as the seat of consciousness, is highly sensitive to any interference with its functions. To a certain extent its circulation is capable of examination through the observation of the fundus of the eye, which is in close relationship to the brain.

Even in cases in which chronic Bright's disease follows acute nephritis, one watches the circulatory system with anxiety, because, when changes are established, the chance of complete recovery is diminished. In acute Bright's disease the heart is temporarily debilitated so that there is often established a blowing systolic murmur at the apex, and the profound anæmia and nervous phenomena that accompany the disease may lead to other functional disturbances of the circulation. These must, however, be distinguished from the changes that take place in the arteries which indicate the transition from subacute nephritis to the chronic general condition. The same change sometimes indicates the establishment of a chronic nephritis in cases of valvular

disease of the heart that have been accompanied by prolonged congestion of the kidneys.

Cardiac hypertrophy is often the earliest detectable sign of chronic nephritis. Abnormal arterial tension may for the moment be absent, either on account of treatment or from some other cause; but when physical examination shows distinct cardiac hypertrophy, we suspect at once a high-pressure case of circulatory disease.

It is probable that an increased flow of urine found in early Bright's disease is due as much to increased blood-pressure as to any definite change in the kidneys. Nausea is another possible result of increased arterial tension, and may therefore indicate the beginning of Bright's disease. Another accompaniment of increased arterial tension is headache, due apparently to increased vascular tension in the head. I would also mention, as one of the early disturbances of high-pressure cases, attacks of indigestion. These are due at this early stage to disturbances of circulation in the stomach, and are not to be confounded with uræmic nausea.

High-pressure cases more often develop in an atypical than in a typical way, and even in their final fatal course may never present the symptoms that one would expect. The early symptoms are often an unhealthy look, loss of strength, and such disturbances of digestion as may be referred to simple weakness. The urine may contain albumin only at rare intervals, so that it may not be detected by anything save systematic observation.

It is fair to say that the early signs of impending changes in the blood-vessels also mean the early circulatory changes of Bright's disease. The first signs of degeneration are manifested by disorder of function. The blood-vessels act as tubes to convey the blood to different parts of the body as it may be most needed. It is this regulating function which first suffers when the tendency to high pressure begins to show itself, so that irregularity of tension is the most important early circulatory indication. The smaller arteries are attacked earliest, and these are the first to show disordered function. Increased arterial tension, or a tendency to it, causes irregularity of blood-pressure, and is early recognized by symptoms indicating irregularities of circulation in particular parts of the brain. This irregularity may give rise to temporary unconsciousness, slight paralysis, or simply to clumsiness of a limb.

The typical high-pressure case, as met with in practical work, is usually one which has gone on to its full development without observation or treatment. The patient presents himself because he has symptoms, or because on some occasion an examination has revealed the chemical or physical signs of the condition. The heart is found hypertrophied, the arterial tension high, and the urine increased. Careful questioning will elicit symptoms of disorder of the cerebral circulation as indicated by a subjective feeling of nervousness, headache, insomnia, or attacks of dizziness, or even threatened aphasia and hemiplegia.

The Blood-vessel Tone-maintaining Function of the Brain.—As we trace the development of the circulation from the lower forms of life up through the scale, we find that the control moves closer and closer to the central nervous system. In the higher forms of animals a tone-maintaining function is easily traced to the medulla, and I believe that, in man at least, an important part of this function is found in the cerebral hemispheres.

It is well-known that there is a tone-maintaining influence originating in the motor areas of the brain that preside over the tonicity of the voluntary muscles. When a stroke of paralysis occurs, due to damage to the part of the brain that presides over the motion of a limb, that limb is paralyzed with regard to voluntary motion, but at the same time there occurs a relaxation, a loss of tone, in the blood-vessels that causes swelling. This suggests the fact that the involuntary muscles were likewise involved in a loss of tone, and would seem strong evidence of this blood-vessel tone-maintaining function. Not only may local blood-vessel tone be affected by

changes that occur in the brain, but also the general tonicity of the whole circulatory system. In all brain conditions, we look for changes in the peripheral circulation. Emotion may cause a rapid rise of blood-pressure. It is said that insane asylums are full of high-pressure cases due to cerebral excitement. In cerebral neurasthenia the blood-pressure is apt to be low.

In advocating the recognition of a blood-vessel tone-maintaining function of the brain it is not necessary to minimize the importance of the centre in the medulla, whose activities in this direction are so well known. It is only necessary to believe that the activity of this centre is dependent upon stimulation received from the brain. A recognition of this function of the brain, which exercises a general control over vessel tone and therefore over blood-pressure, makes it much easier to understand many important disorders of the circulation; and the benefits of certain plans of treatment which experience has proved to be of the greatest value. It explains why exercise of the voluntary muscles has so good an influence over disorders of tone of the involuntary muscles. It makes clear why resistance exercises have vindicated their right to a place in the treatment of disease of the heart. It also reveals the development and points the way to treatment of idiopathic vascular hypertension, a disease the importance of which is becoming more and more recognized every day.

HYPERTONIA VASORUM IDIOPATHICA.—This is *par excellence* the disease of the present day and is looming up as of more and more importance in proportion as it is better understood. The time cannot be remembered when successful men were not stricken down in the midst of their activities by apoplexy or so-called heart failure, but of late years it is increasingly common for those men and women who play the most prominent part in the world and carry the heaviest burden of responsibility, to develop finally disorders of the arteries of the brain or of other vital organs, resulting on the one hand in apoplexy or on the other in Bright's disease. We have attributed these breakdowns too often to chemical causes arising from disorders of the digestive system, or we have regarded them as primarily disease of the kidney, developing in some mysterious way. Too often has alcohol been blamed when in reality it was hardly a factor in the case. Why should it be that persons pre-eminent for the use of their brains, and singled out for the heaviest responsibilities, suffer in the direction of the circulation so much more than those whose occupation is of another character? The reason is to be found in the effect of mental strain in exaggerating that tone-maintaining function of the brain that was discussed in the previous section.

Let us trace the development of such a case, resulting in an attack of apoplexy. A composite picture, drawn from the mental concept of this disease, tallies almost line by line with many concrete examples. The patient is a man of good family history, inheriting sturdy qualities from an ancestry that has developed strength through the successful contest with the difficulties of the development of a new country. He has been well educated and has led a healthy and active youth. From the very beginning, he has been a worker among his fellows and, spurred on by one success after another, by middle life he has attained a position of importance and usefulness. Now his qualities have been recognized, and one burden after another has been laid upon him. He has become a factor in government, in business, in intellectual pursuits, and in philanthropy. Such a man, unmindful of the fact that he is past middle age, and that the body no longer has the recuperative power of youth, continues his work unceasingly, without those relaxations that attract men of a lighter turn of mind. The man feels perfectly well, but a change has taken place in the machinery of his body. The influence from the central nervous system, which maintains the blood-vessels in a proper state of tonicity, has become exaggerated through the overflowing of the mind strain,

and the blood no longer circulates with ease. Now it is hard to keep the blood in proper circulation, but without any manifest symptoms the heart becomes enlarged and still carries on the work. The two factors of arterial contraction and cardiac hyperactivity result in high blood-pressure. This in turn results in structural damage to the blood-vessels in the brain, the kidneys, and elsewhere. Unconsciously, the man is living in constant danger. Some day there arises some incident in his career that leads to an unusual degree of worry or mental strain, and there develops a tendency to inflammation in the already damaged blood-vessels of the brain, the blood clots the circulation, most likely near the speech centre on the left side, and another prominent man has fallen victim to an attack of apoplexy. Sometimes the picture is varied and one of the arteries that supply the heart substance with blood is stopped, and the man drops dead in his tracks; or in another case the kidneys gradually give out. Not infrequently the abdominal arteries show the first indications by terrific digestive disturbance, causing great distention of the stomach with gas and marked irregularity of the heart. This is my mental concept of *hypertonia vasorum*.

Even after any one of these serious accidents, much can be done for a man made of such good stuff, but how much more satisfactory would be the prevention of such an accident by proper medical treatment and a suitable regimen!

I would register a protest against those who decry the use of drugs in circulatory disease, because in all medicine there is no condition in which proper drug treatment is of greater value, and none in which, to my mind, its usefulness seems more easily demonstrated. The remedies must, however, be used with appreciation of the fact that they are to regulate an active mechanism that is always changing in its demands, and that the one needed at one time may be contraindicated a little later.

This implies very careful medical supervision, particularly when the case first comes under treatment. By a process of re-education of physiological processes, control of function becomes easier and easier; and, as the patient becomes familiar with his tendencies, the physician can in a measure yield control. The details of treatment must be worked out for each individual with due regard to the relation of blood-pressure, heart disease, and blood-vessel damage.

The management of high-pressure cases is perhaps the most important part of our subject, as it is also the one in which the greatest advance has been made. The recognition of the functional element in cardiovascular disease marks perhaps the greatest single advance in the appreciation of the therapeutic needs of patients suffering from disorders of the heart and circulation. If we believe that the therapeutic modification of function is of advantage only so long as the effect of our remedies lasts, then we must indeed be therapeutic nihilists, for truly enough we cannot continue indefinitely to use vasodilators, cardiac stimulants, and alteratives. We have faith in the cure of cardiovascular disease because the persistent and patient modification of function by diet, drugs, suitable exercise, and a carefully selected environment finally educates the person's physiological activities so that they act normally after the withdrawal of active measures. This education or re-education, by which functional derangements are removed, holds out hope of a permanent cure of *hypertonia vasorum* and the removal of damaging high blood pressure. It is, of course, most useful before tissue damage has been wrought by the pressure violence to the nutritive vessels of the heart, brain, or kidneys.

In an early case of high arterial tension of nervous origin the important element in physiological re-education consists in training the victim to eliminate worry and a tendency to too great concentration of interest in whatever pursuit is occupying him. Worry is in a measure a habit and can be eliminated by a person of strong intellect, who definitely decides to let events in a measure

take their own course, and the too great concentration on one's occupation is a self-indulgence that often ignores the importance of other things and the legitimate claim of the lighter things of life upon the attention.

The business man should be content with a reasonable financial success, and the professional man with a reasonable degree of distinction. In a paper read before the New York State Medical Society in 1907, Dr. H. L. Elsner pointed out that physicians themselves should be on their guard lest they suffer from the evils of high tension in their own circulation. The patient should deliberately eliminate under the advice of his physician all unnecessary burdens of responsibility. If the man or woman has occupied a position of trust, and has given that devotion to work that has led to hypertonia in the circulation, he or she is certainly entitled to pass the burden on to some one else. Often enough, when unnecessary burdens are thrown off, it is perfectly possible to take care of what are left. The world is not to be reformed in one generation, and no one was ever meant to carry the burdens of the universe.

Next to the elimination of worry and undue concentration of mental effort comes the question of nutrition and diet. Many persons consider themselves undernourished, when in fact the opposite is the case. A critical examination of the blood and urine often shows distinct evidence of an excess of food in persons who are seeking to be built up by physical rest and a diet selected for its nutritious qualities. When this is the case, the food should be restricted in quantity—sweets eliminated, and meat greatly reduced. The popular prescription of withholding from these patients all food that has contained blood may be extreme, but it is in the right direction. Third, but not least in importance, is the matter of physical exercise. Here we come upon the relationship, which I have often traced, between the tone-maintaining function over the voluntary muscles, and a possible similar function with regard to the involuntary muscles. Exercise should be carried on systematically, whether the patient feels like it or not. A distaste for physical exercise often goes with this condition, and must be overcome by emphatic instructions by those responsible for the welfare of the patient. There is, undoubtedly, some advantage in the resistance movements, though massage does not seem suited to many patients with high blood pressure. It has seemed to me that the resistance movements were valuable in removing overtone through some connection with the tonus of the voluntary muscle. While the patient is under treatment, or re-education, the circulation must be regulated as far as possible by drugs that improve the muscular tone of the heart and those that overcome an excess of tone in the blood-vessels. These must be given under skilled direction of some one who has the knowledge and authority to regulate the time, quantity, and nature of the medication almost from hour to hour, to meet the manifestations of the pathological physiology of the disordered circulatory system. In some instances a few weeks will counteract the commencing high tension, and the individual may go on for years without its developing again. In more severe cases, several months are necessary. In cases that have lasted a long time a year is necessary for the physiological re-education. The intelligent co-operation of the patient and the friends of the patient is absolutely necessary. In difficult cases, the work is most discouraging at first, though often enough after a few weeks the beneficial results become rather suddenly apparent to every one. Where there are distinct evidences of broken compensation, treatment must, of course, be commenced by keeping the patient in bed, but these patients can often least afford the debilitating effect of bed treatment, and the sooner outdoor treatment can be instituted the better. An attack of apoplexy does not preclude the possibility of good results from physiological education in high-pressure cases, but, of course, makes the problem more difficult. Particularly is this true when, as is often the case, there is a distinct tendency to depression of spirits, approaching

melancholia; for the mental tension that goes with this stage makes the high tension hard to control. Physiological re-education should begin early, but unfortunately this newly recognized condition of idiopathic vascular overtone is not generally enough recognized for the necessity of such active treatment to be appreciated as often as it should be.

In its early stages it is a disease without symptoms because the heart first brings into play its reserve force, and then painlessly becomes enlarged, and the severer accidents of the development of Bright's disease, of apoplexy, or of heart failure have to do only with the fully developed condition. It behooves every one, particularly if over fifty, to have the vital organs inspected at regular intervals, so that overtone may be early recognized and prevented.

The Use of Nitrites.—When Brunton applied amyl nitrite to the treatment of angina pectoris, he achieved a signal triumph in therapeutics. Not less was the triumph of the more gradual application of the nitrites in general to the treatment of vascular spasm. These were first well used by those who had witnessed their development and were familiar with their philosophy and limitations. Unfortunately, the student, coming later upon the field of medicine and finding the nitrites in general use for vascular disease, jumped naturally to the conclusion that they were the remedies *par excellence* and used them in a routine way in the treatment of these cases. The observation of this fact makes it seem useful at this time to emphasize the necessity of conservatism in this matter. It is a trite saying that we should always treat the patient and not the disease, meaning by this that we must carefully recognize the exact physiological and pathological conditions present, and so influence them as to bring about the cure of disease. Patients differ widely in their behavior under the nitrites, and for that reason every case requires physiological study to determine the amount of drug necessary and how it should be applied. To apply vasodilators without also instituting hygienic measures to reduce the irritability of the heart and restore the exhausted or disordered nervous system is to overlook an important element in the problem of cure. The necessity for the use of vasodilators is diminished in proportion to the intelligence and success attending these accessory measures.

In Bright's disease there is probably some substance circulating in the blood that irritates the muscular coats of the vessels and causes contraction. This, with the physiological attempt of the heart to carry on the circulation, again brings about high tension. When high tension antedates the onset of nephritis it may well be supposed that the tension has something to do with the production of nephritis.

A physiological increase of blood-pressure is caused whenever there is nervous, muscular, or physiological exertion. Prolonged nervous strain, such as that met with in an exciting business career, or in prolonged dissipation, keeps up a tendency to tension that is particularly apt to lead to arterial degeneration. Muscular action is less prone to produce damage, and probably does so only in rare instances of long training and severe contests of strength. The reason for this is that exercise is accompanied by natural dilatation of the arterial circulation, improved nutrition, and relief afforded by perspiration. The physiological activities of the body are usually accompanied by too slight a stimulation of the circulation to count for much in health, but are worth considering in disease.

In the case of a person suffering from abnormal tension, it is especially important to do away with mental strain and responsibility. Such a person should not indulge in violent exercise, but is benefited by slow exercise. Food should be moderate in amount, taken at frequent intervals. Sugar and alcohol should be done away with entirely, if possible, and meat used only in limited amount.

When the vasodilators are given it is to produce a

definite physiological effect which is capable of being appreciated by the observer. The dose required to produce this effect differs widely in different individuals and under different circumstances. In a large number of cases the remedies are now so given that no effect whatever is produced. Crude therapeutic thought is responsible for this. The idea is conceived that the nitrites are good for kidney and heart disease, and so they are administered with the hope that the patient may be benefited thereby. If improvement takes place the medicine receives the credit, whether it has done its work or not. The word "conservatism" means more than caution, more than small dosage. It means the working out of the possibilities of the remedy and its application in such a way as to fulfil its broadest mission, so that it may not be wasted or abused—wasted when used in non-active doses and abused when used too often or in too great quantity. With the vasodilators a careful regulation of the dose is of vital importance, for their final action may be dilatation and paralysis of the heart through a complete breaking down of that great power which moderates all muscular activity.

When nitrites are used it is also of the utmost importance that the preparation selected should be reliable. I have known patients to take for a long time tablets supposed to be nitroglycerin which were frequently found to be inert. When no benefit is obtained in conditions in which nitroglycerin is clearly indicated, this may be fairly suspected. As a test, one of the tablets should be given to a healthy person, who should immediately feel the throbbing in his head due to the dilated blood-vessels and the stimulation of the heart. If no effect is felt, a new preparation must be sought and this tested. The one-per-cent solution of glonoin is probably more reliable, but is not nearly so convenient for patients as the tablet. I have found granules of nitroglycerin, gr. $\frac{1}{32}$, very convenient.

Cases must be studied from time to time by the withdrawal of these drugs, and by the substitution of other drugs of a different class. Particularly is it important in every such case to know from actual observation the effect of digitalis in such doses as bring about distinct physiological phenomena.

But few diseases can be treated by specific measures, and cardiovascular disease is particularly remote from such an ideal. The end which drugs accomplish is such control of the circulation as will tend to benefit the condition of the tissues, or the prevention of the condition of these tissues from working injury to the body as a whole. The management of cardiovascular disease is like the running of an intricate machine. The physician must study the machine itself and learn all its resources. He must know the use of every tool and the effect of the turning of each screw. It is no abuse of the privileges of the physician to study his cases therapeutically by testing from time to time the effect of different classes of drugs, though he return after each trial to the original plan of treatment. It is the height of arrogance to assume that his inductive reasoning can plan for each case a permanent course of management. Such action would lead only to humiliation and disappointment. How exasperating it is, when for a long period of time, on theoretical grounds, we have abstained from the use of such a drug as digitalis, to find, some time or other, that our patient has taken it through the advice of the corner druggist and has received appreciable benefit from it! Of course, we know very well that the corner druggist had no right to experiment, but perhaps the risk was worth taking, after all.

There is a particular form of pulse in which nitroglycerin is not so valuable as a number of other drugs. This is a high-tension pulse, with persistently rapid heart action. In these cases, I have sometimes seen the greatest benefit from the use of digitalis. Nitroglycerin has a twofold action in stimulating the heart and dilating the blood-vessels. Digitalis has a twofold action in slowing the heart and contracting the blood-vessels. Theoretically digitalis would not act in these cases; but

practically in a case of nephritis with a high tension and rapid pulse, digitalis will often show its controlling action upon the heart in greater degree than any of its other effects, and in that way bring about a slower pulse with less apparent tension. At the same time, digitalis will clear up congestion of the kidneys and cause a better secretion of urine.

Even when tension does exist in cardiovascular disease with nephritis, it should be realized that some tension may be desirable. As time goes on in such a case, the greatest danger to be feared is a too great lowering of the blood tension, with its accompanying congestions and effusions. In the presence of symptoms indicating disturbances of cerebral circulation, such as numbness or awkwardness of one of the extremities or slight difficulty in speech, the vasodilators are imperatively needed. Sodium iodide has also an undoubted power to postpone paralytic attacks due to the plugging of blood-vessels.

A word as to the possibility of recovery from cardiovascular degenerative disease. The heart symptoms are those of myocarditis and the kidney symptoms those of chronic nephritis. The tendency of the blood is to become of poor quality. Every one knows that under ordinary circumstances a person starting with this form of disease has a tendency to become worse. However, I do not believe that this need always be the case. With a properly planned regimen and the possibility of carrying it out, and with careful medication and other therapeutic measures, the heart may recover its tone so that all symptoms of degeneration will disappear, and the kidneys may settle down to do their work according to a particular plan, but well enough for the maintenance of health.

It is hard to prove the regeneration of kidney tissue, though the physiological hypertrophy of one kidney when the other is removed leads to a belief in its possibility. Certainly there are many persons passing a large quantity of urine of low specific gravity and with a slight trace of albumin, who maintain year in and year out signs of health. Their heart, blood-vessels, and kidneys have readjusted themselves and, though bearing the scars of disease, are carrying on the functions of the body in a satisfactory manner. I have pictured this condition because it is extremely interesting to decide in these cases how much we should intervene with drugs to alter the heart action or relax the blood-vessels. It seems to me that in the absence of symptoms sodium iodide will accomplish the best purpose and that the use of the nitrites should be limited.

Management of Secondary Low-pressure Cases.—The treatment of low arterial tension which is secondary to long-existing high-tension conditions has two elements—first, the correction of circulatory errors by the action of drugs which have the power to modify physiological forces in various parts of the circulatory circuit, and, second, the restoration, as far as possible, of the health of the tissues upon derangement of which the trouble often rests.

In diseases of the circulatory apparatus attention is too often concentrated upon the first. In instances of temporary embarrassment, or of extra demands on account of complicating diseases, this first element becomes of supreme importance, but in the long run it is the second element upon which success in the care of circulatory disorders is dependent.

In this connection, it is important to differentiate between the symptoms and the disease. Dropsy of the dependent portions of the body is a symptom which does not always demand treatment. If of moderate degree, and dependent upon well-understood causes, it is often the part of good judgment to undertake the second element of treatment, neglecting for the time being the symptom, the removal of which would require intervention in the physiological activity of the heart, such as might neutralize treatment directed to the circulation as a whole; indeed, there is often much harm done in such cases by violent attacks upon symptoms.

Most writers on circulatory disease have passed over with scant consideration the management of cases with general cedema and steadily progressive symptoms, which, if not checked, uniformly lead to a fatal termination. It is unscientific to disregard these cases in considering various forms of treatment at length, dismissing them with a single clause. This is frequently done in speaking of the Nauheim treatment, progressive cases being usually spoken of as unsuitable. There is always the possibility in any particular case that we may be mistaken in our estimate of it, and the patient is entitled to the treatment even at the risk of discrediting the system by the limitation of results because of the severity of the case.

In primary low arterial tension the heart muscle is in a position to recover its tone if depleted by acute disease, or to develop a compensatory hypertrophy if overtaxed by defective valves. In secondary low arterial tension the heart has already for the time being exhausted its power of compensatory hypertrophy, and while the tendency to resistance in the arteries persists, there is no adequate response on the part of the heart.

Little is gained symptomatically in extreme cases by the use of vasodilators, because the blood-pressure is already low. Little is gained by digitalis, because the heart-muscle is not in a position to respond. The combination of drugs of the digitalis group with drugs of the nitrite group produces a certain amount of symptomatic response, but in the end does not produce permanent results unless combined with measures that will hold the advantage gained. Excessive drugging is a mistake. A single large dose of digitalis at night is often better than divided doses. A good fluid extract put into a capsule and swallowed at bedtime, the dose being determined by experiment, has often proved very satisfactory. Attention to the digestive organs is of the utmost importance. Milk is often badly borne and should be replaced with the most nutritious food that will agree with the patient.

As often as possible, these patients should be put upon a regimen directed to the improvement of nutrition and to the healthfulness of the body in general, such as hydrotherapy in the form of warm saline baths, a nutritious diet without too much regard to theories as to gout or disease of the kidneys, and exercise in the open air up to the point where dyspnoea interferes.

We are dealing often enough with dangerous conditions, and it is not possible to compare the result in a particular case with what it would have been under other circumstances. A man must be of limited experience indeed who has not seen such a patient do better when disregarding advice that planned treatment of such a condition by prolonged rest in bed, restricted diet, and excessive drug therapy.

Secondary low arterial tension is the final result of many causes acting along the line of those forces which tend to the termination of life in the natural course of events, hence it is to be combated, not by drugs alone, but by all those methods that are known to remove cachexia, and restore tone to the blood and solid tissues.

Louis Faugères Bishop.

ASIATIC CHOLERA.—(Synonyms: Epidemic cholera, Cholera asphyxia, Algid cholera, Malignant cholera, Cholera spasmodica, Pestilential cholera, Pestilential asphyxia, Oriental cholera, Choleric pestilence, Indian cholera, Ganglionitis peripherica et medullaris, Tri-splanchnia, Hyperanthrax, Morbus oryzeus [because supposed by Tytler to be due to damaged rice], Trousseau-galant, Cholera gravior, Vishucki or Vishuchiki [by Hindoo physicians], Haouwa [tornado] in Bagdad.) (For a wider discussion of terminology, see Macpherson, "Annals of Cholera," chapter ii., ed. 1884.)

The derivation of the word cholera is usually from *χολή βέω* (flow of bile), or *χολὰς βέω* (intestinal flux), but the correct one is probably that given by Jobard, of Brussels (*Gaz. Méd. de Paris*, 1832, p. 389), who con-

siders the term to be made up from two Hebrew words, choli-ra (or morbus malus).

Asiatic, or epidemic, cholera is an acute infectious disease that is endemic in certain parts of India, and that has during the last century advanced out of that country to other parts of the world, where, in its epidemic form, it has produced great loss of life. It is characterized by its great fatality among the communities to which it may be transported, by the apparent ease with which it has been carried from place to place, and by its invariably following the lines of travel in its march from one place to another. It is distinctly a disease of the gastro-intestinal tract, produced, primarily, by a micro-organism and attended with secondary symptoms, due to the absorption of toxic principles elaborated during the development of this micro-organism.

There is only a difference of degree between cholera, choleraic diarrhoea, and cholérine—the disease is the same in all these forms provided that they are accompanied by the activity of the spirillum of Koch. So far as true cholera and cholera nostras are concerned, there is a very great similarity, or rather there may be, between the clinical symptoms of the two diseases, but the differentiation may be easily made by the isolation of the specific spirillum of the former. The same thing is true in regard to the differentiation of true cholera from an attack of indigestion, which, if severe enough, may take on many of the characteristics of true cholera. Cholera nostras is a seasonal disease and is not transportable, and it has been known for ages. True cholera made its first advance out of India in 1817, and since that time has been seen periodically in Europe. In all cases it has followed the line of travel, and has never been seen to be distributed in any other way. Therefore true cholera never makes its appearance except after other cases have been seen that might excite suspicion, while cholera nostras appears only in hot weather, in sporadic cases, and dies out if the weather becomes cooler.

The period of cyanotic chills, although one of the most striking in both diseases, gives no special indications for differential diagnosis, for the same thing is seen as an accompaniment of many other diseases, as acute catarrhal diarrhoeas, acute poisonings, etc. The prodromic period exists in cholera nostras practically always, but not nearly always in true cholera.

The period of reaction is of importance in differential diagnosis. In cholera nostras it is usually benign—if the patient escapes the violence of the first attack, convalescence is as a rule easy and rapid; with true cholera, on the contrary, convalescence is exceedingly dangerous—full of pitfalls, and may terminate fatally at any time.

Mention of the disease is made in Sanscrit and Chinese writings. It is spoken of by Hippocrates (Epidemics), and successively by Aretæus, Celsus, Galen, Caelius Aurelianus, Aëtius, Paulus Æginatus, and Alexander de Tralles. All of these writers, with many others, refer to affections resembling the cholera, but it is not until the seventeenth and eighteenth centuries that we find descriptions of the epidemic disease. Genuine epidemics, analogous to cholera, are described by Rivière, who made his observations at Nîmes in 1564, and by Zacutus Lusitanus, who saw several in different parts of Europe in 1600. The most remarkable accounts by authors of this epoch are those of Willis ("Opera Gen." 1680, t. xi., p. 74), describing epidemics in London, in 1670, of what he called "dysenterica aquosa epidemica," of Thomas Sydenham, in 1669-76 ("Oper. Med.," Geneva, 1723, pp. 106 and 184), and of Torti ("Therap. Spec.," liv. iii., cap. ii., and liv. iv., cap. j.). Bontius ("De Medic. Indorum," Lugd. Batav., 1642, p. 136), Delon ("Voyage aux Indes Orient." Amsterdam, 1684), and Thevenot ("Voyage aux Indes Orientales," Paris, 1689, tom. iii.) observed and described epidemic cholera in India. In 1761, Donald Monro ("An Account of the Diseases in the British Military Hospital in Germany," London, 1764, p. 97) saw an epidemic of cholera in Westphalia; as did Agton Douglass and Bisset, in 1768, in the north of England and in Scotland. Harlem ("Die Indische Cholera"

1831, t. i., s. 144) quotes many dissertations upon the disease, but it is not until the last century that we have a clear account of the transportation of the disease from place to place. From 1817 it seemed to take on a new power of travelling, and owing to this spread the opportunities for its study have vastly increased. The new methods of intercourse and commerce were probably responsible for the appearance of the disease in Europe—not any new property which it developed.

A study of the history of the epidemics that have occurred outside of India will easily demonstrate the facts in regard to the ways by which the disease is transported from place to place.

HISTORY OF EPIDEMICS OF CHOLERA AND THEIR LESSONS.—The dispute is active as to whether true cholera existed in India before its appearance outside of its limits in 1817, but the probabilities are all in favor of its having done so, epidemics of considerable proportions being reported in the eighteenth century; the especial point that seems to be changed in its nature being that it then seemed to take on the property of migration. Whether this was in reality a new property, or whether, as is much more probable, it was simply brought to the notice of Europeans by their being first attacked by it, is an unsettled question. There is no doubt, however, of the very great influence exerted upon its spread by the great pilgrimages to the various shrines of India; nor is there any doubt that the sole home of true cholera—the one place where it is present all the year in an endemic form—is the delta of the Ganges. There are also certain places in India, Indo-China, China and Japan in which it seems to be present nearly all the time, but it certainly is not endemic in Persia, on the borders of the Caspian Sea, nor in Mecca.

From this one place in which it is endemic, cholera has always been transported to Europe in the steps of the traveller and along the routes of commerce; neither wind, moisture, electricity, nor any of the forces of nature have taken any active part in the actual transportation of the disease, although unfavorable climatic and hygienic conditions, of course, may play a favoring part in the development of the disease, after the arrival of its cause.

EPIDEMICS OF CHOLERA.—Cholera has made five appearances in Europe—in 1830, in 1846, in 1865, in 1884, and in 1892. Each one of these appearances was a great epidemic.

There had been also, in 1823, in Astrachan, a small epidemic of cholera, important because it traced the route that the succeeding invasions would follow. Leaving Persia, where it prevailed in 1822, cholera invaded the southern provinces of Persia, forming the southern shore of the Caspian Sea. After some ravages, it became quiescent during the winter of 1822, to reappear in April, 1823, at Recht. From this city, following the western shore of the Caspian Sea, it crossed the Russian frontier in June, at the little town of Astara. From Astara it reached Lenkoran on the 29th of June. On the 11th of September it was seen at Bakou, and on the 23d at Astrachan, where it soon disappeared.

The First Epidemic.—The epidemic of 1830 had the same origin. Ghilan and Mazanderan, the two Persian provinces before invaded, were attacked in 1829. The disease was quiescent during the winter, but appeared in the spring in Ghilan and in the little port of Enselli, situated several hours' journey from Recht. As in 1822, the cholera followed the western border of the Caspian Sea, and showed itself about the middle of June, 1830, at Salian. Taking here two different directions, on the one side it appeared at Bakou, Kouba, and Derbent, and invaded Astrachan; on the other, following the whole valley of the Koura, it advanced toward Tiflis, passing by Elizabethtopol, and spreading throughout the whole of the Caucasus. In this way it reached successively the neighboring regions of Astrachan, and advanced up the Volga. On the 4th of August it was at Saratow, thence extending into Russia, and reached the other European States.

This epidemic, by certain extremely interesting pe-

culiarities, demonstrated from the very first the transportability of cholera.

The Second Epidemic.—In 1846, after having reached Salian by a course identical with the preceding, cholera was seen on November 8th in the city of Chemacka, a short distance from Salian. It was in Bakou and at Derbent in December. Forgotten during the winter, it appeared in April, 1847, in the districts of Derbent and of Kouba, and at Tamir-Khan-Choury. From thence it was transported by sick soldiers to the mineral waters of Kisliar. The disease was disseminated among the Calmucks scattered over the steppes near the Volga.

On July 15th it appeared at Astrachan, and advanced at the same time toward Tiflis. From Tiflis it reached Koutais, and was soon carried to Trebizond.

North of Tiflis, the cholera followed the great military road that crosses the Caucasus at the height of seven thousand feet, and toward the end of July it existed at Stavaropol, on the other slope. (It is to be observed that before reaching Tiflis, the cholera entered Persia by the great routes of travel that pass from Bakou, by Erivan, Natchichievan, Djoufa, Ordoubaz, and on toward Tauris. On the one side it attacked the region of the Black Sea, and invaded all its ports; on the other, it passed through Russia, Germany, France, and Italy.)

A striking thing about these epidemics, aside from the exact places that they attack, is their progress by successive stages—a form of advance that is always the same, and which is a trait common to all the epidemics of cholera that have followed the land route. This second epidemic persisted until 1855.

The Third Epidemic.—The great epidemic of 1865 was the first one appearing by the sea route. It demonstrated that the danger is not localized on the Caspian Sea, but that it is also present on the shore of the Red Sea. Its appearance by this route upset all the doctrines that had been held until that time, and the panic that it produced in Europe resulted in the first conference at Constantinople. It is interesting to follow in some of its phases the course of this epidemic, because its influence has been great. It started from Mecca, having been brought into that city by ships coming from India filled with pilgrims. Toward the end of April it broke out in Mecca and at Medina. The mortality increased very greatly during the three feast days at Arafat. More than thirty thousand of the pilgrims died of cholera, and the progress of the disease showed that *everywhere it accompanied these pilgrims*. Egypt, by reason of its proximity to Mecca, was the first country attacked.

From May 19th to June 10th ten steamers landed from twelve to fifteen thousand pilgrims at Suez. By false declarations from the captains they were passed at Suez, although the *Sydney*, an English steamer, had lost a number of cases during the voyage. The first steamer, landing May 19th at Suez, had thrown its dead into the sea. On the 21st, cases appeared at Suez, and among the number were the captain of the vessel and his wife.

June 2d, the first case appeared at Alexandria, and in two months cholera had four thousand victims in Alexandria, and in Egypt, in less than three months, it produced the death of more than sixty thousand individuals. The foreign population emigrated *en masse*, and carried with them throughout the entire world the germs of the disease. Europeans and Levantines, to the number of from thirty to thirty-five thousand, started for all the ports of the Mediterranean, and cholera developed at Constantinople, at Smyrna, at Beyrout, in Mesopotamia, and at Odessa on the Black Sea, and was carried to New York and Guadaloupe by steamers, appearing in the port at the same time that the steamer landed its passengers.

Its importation into New York was as follows: The *Atlanta*, an English ship, left London on October 10th with a cargo of merchandise and forty passengers. The sanitary condition of London was at that time excellent. Reaching Havre on the 11th, where it remained one day only, it embarked five hundred and sixty-four new passengers, mostly Swiss, who had all passed through Paris, where, with certain exceptions, they had remained at

least a short time, and where at the same time cholera was raging with great intensity. Two German families had stayed in Paris at the Hotel of La Ville de New York, and five days at the hotels of the Weissen-Lamm and Hultgarderhof. Some emigrants that had arrived several days before in these last hotels had fallen suddenly ill. The steamer sailed on the 12th, and on the next day there was a death from cholera of a child in the family coming from the Weissen-Lamm Hotel. Five other deaths followed on the 14th, the 16th, the 18th, the 19th, and the 22d, in the family that had stayed at the Hultgarderhof.

On the arrival of the *Atlanta* the surgeon declared 60 cases of cholera, and 15 deaths during the voyage. Two deaths occurred in port, and of the 142 patients sent to the Marine Hospital from November 6th to 19th, 6 died, which makes a total of 23 deaths. The *Atlanta* was immediately isolated in the lower bay, and after ten days of quarantine all the sick were removed, and, thanks to these measures, New York was preserved.

There were also importations in 1866 by the steamers *Virginia* and *England*.

The epidemic of 1865 ceased in 1874, and there was no other case seen in Europe until 1884, although there were interesting manifestations in other countries and on the sea—interesting from the point of view of the transportability of the disease.

The Fourth Epidemic.—The epidemic in Egypt in 1883 was no surprise to those who knew the sanitary condition of the country. Cholera appeared at Damietta toward June 19th or 20th, possibly a little earlier, and its explosion at this time is ascribed, certainly by the French, to the suppression of all sanitary precautions, including quarantine, by authority of the British Government. This epidemic at Damietta increased for about fifteen days, remained stationary for about five or six days, and then diminished just as speedily. It was almost extinct a month after its appearance, having claimed from two thousand to twenty-five hundred victims. The spread of the disease throughout Egypt was manifest and rapid. (An interesting account of how this epidemic reached Damietta is given in Proust's work on the "Defence of Europe against Cholera," Paris, 1892, p. 7.)

Cholera had not yet died out in Egypt, before the news came that it had broken out among the pilgrims to Mecca, and there has been much discussion as to the origin of this epidemic.

In 1884 a number of vessels left the extreme East, and had cases of cholera on board during their voyage; but, by reason of the precautions taken, Egypt and Europe escaped the danger at this time.

The first case of cholera seen at Toulon occurred on June 13th, on the ship *Montebello*; a second case on June 14th; a third on the 18th, on the *Jupiter*, near the *Montebello*; a fourth, also on the 18th, on the *Montebello*; a fifth, June 20th, on the *Alexander*, which was also placed near the *Jupiter* and the *Montebello*. After the 21st the disease spread through different quarters of the city, and it is thus shown that it did not make its appearance at Toulon in the city, but just outside.

Its importation into Marseilles occurred by the appearance of the first case on June 27th, in a young man, who had three days before come from Toulon. The next case, which occurred on June 28th, was that of a man who lived in the same neighborhood; and from this time onward the disease continued to spread.

In Paris there appeared two cases on the 13th or 14th of July, but the epidemic did not really begin until the 4th of November.

In Brittany the first case was not observed until September 20th, at Concarneau. Other ports were successively invaded.

Algeria was attacked in 1884, and there was a slight recurrence in Algeria and in Tunis in 1885.

Cholera was brought to Italy in 1884 by the Italian workmen, who, to the number of more than eight thousand, returned to their country after the extension of the cholera to Toulon and Marseilles. The province of

Cuneo, in Piedmont, was the first one attacked, on June 27th, and the disease spread successively to different parts of Italy, to Genoa, Naples, Venice, Sicily, and so on.

It appeared in Spain, in the month of August, in the province of Alicante, and ceased toward the middle of October, reappearing in the middle of February, in the district of Gandia, raging through the month of June to the month of December, 1885, and producing a considerable mortality. It is remarkable that it attacked especially the small towns more than the large cities. The Commune of Aldea de San Miguel, with only five hundred inhabitants, lost more than half of them in thirty-six days.

Cholera also appeared on the Adriatic shores of Croatia, at the end of 1885, and in 1886 on many points of the Austro-Hungarian shore in Istria and in Dalmatia.

The comparison of the mortality in France, Italy, and Spain is interesting. In France and Algeria together there were 13,000 deaths in a population of 39,000,000—1 in 3,000 inhabitants. In Italy there were 35,000 deaths in 26,000,000, that is to say, 1 death in 600 inhabitants. In Spain there were 180,000 deaths, among 17,000,000 inhabitants, that is to say, 1 death in 100 inhabitants. So it appears that Italy was attacked five times more severely by the epidemic than France, and Spain six times more severely than Italy, and thirty to forty times more severely than France.

Much has been said about the immunity of Portugal during the epidemic of 1884 and 1885 in Spain. Many reasons can be brought forward for this, viz., the slight tendency of the Spaniards to take refuge in Portugal, the geographical conditions, and finally, the prophylactic measures taken at the frontier.

In spite of the imperfect quarantine and incoherent measures prescribed by the governments of South America against the vessels coming from Europe, a ship from Genoa, the *Perseo*, carried cholera to Buenos Ayres, and the disease spread into the Argentine Republic, Uruguay, and Chili.

From 1884 to 1886, a period of three years, more than twenty vessels coming from the extreme Orient to Europe, on passing through the Red Sea and the Suez Canal, had, either at the moment of their departure or during the voyage, cases of cholera.

The Cholera of 1889, 1890, 1891, and 1892 (the fifth epidemic).—In 1890 cholera appeared in Irak-Arabi, in Mesopotamia, in Persia, and in Syria, where it had not been seen for almost twenty years. It had been imported into the region bordering on the Red Sea and into Mecca, where it had not been since 1883, and it was observed in Spain, where it had been extinct since 1885.

In summing up what we know of the origin of cholera in Irak-Arabi and in Mesopotamia in 1889 and 1890, the following must be our conclusions:

It is very difficult to admit that the cholera of Irak-Arabi can be attributed to the revival of the old epidemic of 1871, and if this hypothesis be excluded, we are obliged to accept the idea of importation, and it is only possible to think of one portal of entrance, the Persian Gulf, and one source in India, namely Bombay and its environs.

We know from other sources that during and before the appearance of cholera in Irak-Arabi the mortality of this disease in Bombay and its environs reached the enormous number of more than six hundred deaths a week. The condition of the vessels of the British India Company, that alone regularly frequent the Persian Gulf, bring passengers there, and frequently bring pilgrims from India, has been, to say the least, suspicious. Everything points therefore to the conclusion which bears every appearance of truth that the cholera penetrated into Irak-Arabi through Chat-el-Arab. The importation was performed in this way much more probably than by any other means.

In regard to the epidemic of 1890-91 in Hedjaz, Proust offered to the Committee of Hygiene the following conclusions which were accepted: (1) The cholera of Cameran was imported by an English vessel coming from In-

dia; (2) the cholera of Hedjaz appears to have been brought by the sea route; (3) the pilgrimage to Mecca is a constant menace to the health of Europe; (4) the measures prescribed for the government of the pilgrims to Mecca have not prevented the cholera from developing, and it is therefore necessary to perfect these measures; (5) the prophylactic measures prescribed by the Alexandrian Conference at the time of the return of the pilgrims, have this year prevented the disease from gaining a foothold in Egypt and in Europe. There is reason, therefore, for continuing this conference and for giving it more authority and making it in reality international. There is also reason for increasing the means for isolation and disinfection on the Red Sea.

The epidemic which appeared in Spain in the month of May, 1890, and lasted until the end of November, gave rise to much discussion in regard to its origin, a discussion that reached no final conclusion.

In 1890 cholera also appeared in Japan, beginning in June and lasting throughout the year. Over 46,000 cases were reported. The epidemic of 1892 appeared first in Southern Russia and thence spread to isolated parts in the north of Europe, notably Hamburg, where it continued, with declining severity, into 1893 and 1894.

In September, 1892, 10 cases, with 8 deaths, occurred in New York, being imported from Hamburg, or probably derived from such imported cases, and 73 cases, with 43 deaths, occurred in the harbor, together with 56 suspicious cases of disease thought to be cholera. In 1893, 23 cases, 4 fatal, occurred in the harbor, and one death, verified by bacteriological examination, took place in Jersey City, where there were also 6 deaths following a disease clinically diagnosed as cholera. Since then no cases have occurred in this country.

In 1895 there were serious epidemics in China and Japan, over 12,000 cases, with over 8,000 deaths, being reported from the latter country.

In 1896 cholera appeared in Russia, Turkey, Egypt, and a few cases in Austria. During the years from 1897 to 1901, inclusive, cholera does not appear to have spread beyond the regions where it is endemic, except a few cases imported from those places.

In 1902 cholera assumed epidemic form in Mecca, Turkey, Russia, Japan, and China. There were also a few cases in Egypt and other southern Mediterranean countries. In the Philippines, between March 20th and the end of October, over 4,200 cases, with more than 3,300 deaths, occurred in Manila, and in the provinces outside of that city over 102,000 cases, with between 66,000 and 67,000 deaths. Since that time, and into 1903, cases of cholera have occurred in these islands. The first case came from Hong-Kong.

TRANSPORTABILITY AND MEANS BY WHICH THE DISEASE IS TRANSPORTED.—The transportability of the disease is demonstrated by, first, the facts in regard to its propagation after it has been imported; second, by the efficacy of certain measures of prevention; third, by the general march of epidemics of cholera; and fourth, by the development of epidemics in the infected localities.

1. *Propagation.*—Brochard, in "Du Mode de Propagation du Cholera," Paris, 1861, reports a very large number of observations favoring the idea of the transportability of cholera, and the number of instances proving this is so great that they need only to be spoken of to be accepted.

An illustration may be taken from the article by Huette, in the *Arch. Gén. de Méd.*, 5th series, vol. vi., p. 571.

In speaking of cholera in Chatillon, he says that the first case was observed in the Faubourg du Puirault, in a workman, thirty-five years old, who was attacked immediately after his return from Oussoi, where he had gone to take care of his parents who were sick with the disease. His neighbors were very soon attacked, and the epidemic invaded the entire Faubourg du Puirault, where it remained concentrated for some little time. Finally the inhabitants, frightened by the disease, scattered through Chatillon, and the cholera appeared

indiscriminately throughout the city. The instance is interesting, because while the inhabitants remained in the Faubourg du Puirault, the disease stayed there, whereas, as soon as they scattered, it spread with them throughout Chatillon.

Another instance, interesting as an example of the transmission of the disease by clothing, is given by the same authority, in speaking of the Commune of Oussoi. Madame Bresson, of the hamlet of Moulineuf, near Oussoi, a precinct free from cholera, received a boarder from Paris, June 27th, who on the next day showed the first symptoms of cholera, and died on July 3d. Some days after, a child of this woman was attacked and died on July 13th. On the same day Madame Bresson herself was taken sick, and died on the 17th, after having been taken care of by two neighbors named Sahau and Moret, who died, one on the 16th and the other on the 24th. The husband of Madame Bresson died on July 26th. Madame Burette, who lived in the extreme end of the hamlet, washed the linen of the two women, Sahau and Moret, and was attacked with cholera. In this way, an epidemic was started that carried off eighteen persons in a very short time. Before the arrival of the person from Paris no case had been observed in this hamlet, that had been spared by the cholera both in 1852 and in 1849. Dr. Huette calls attention to the distribution of this hamlet of Moulineuf, which is composed of ten little collections of houses, separated by great distances. No cases of cholera were observed excepting in three of these collections of houses—first, that occupied by the Bresson and Sahau families; second, that occupied by the Moret family; and third, that occupied by the Burette family. The third collection of houses was situated at the extremity of the hamlet. No case of the disease was observed in the other houses, of which the inhabitants had had no connection with these three families.

Proust (*loc. cit.*, p. 165) quotes an occurrence illustrating another series of facts.

In 1854 the French army was collected at Varna, a short distance from the English army. Some detachments remained at Gallipoli, the original place of debarkation. There were, besides, a small Anglo-French force of occupation in the Piræus, and also some detachments at Constantinople. The armies were reinforced practically every day by new arrivals. The sanitary condition was satisfactory in all respects. On July 5th the packet *Alexandre* arrived at Constantinople, having left Marseilles on June 26th with five hundred men of the Fifth Regiment of Light Infantry, coming from Montpellier, and having passed through Avignon, where cholera was raging. It appeared on board, and three men died during the voyage to the Dardanelles. Four cholera patients were landed at the Piræus, where the cholera broke out immediately, and made great ravages. The troops were disembarked at Gallipoli, where two new cases of cholera were immediately sent to the hospital, and the ship, having only a few passengers on board, sailed for Constantinople, where a quarantine was imposed on it. On the other hand, it appeared that previous vessels sailing from Marseilles had already suffered from cholera, and that one of them had landed a patient in the military hospital at Constantinople. On July 15th, after new arrivals of cholera patients, the disease spread at Gallipoli, and there appeared in the military hospital of Constantinople a choleraic focus. Fauvel, struck by the danger, proposed, and had adopted by the Council of Health at Constantinople, a momentary interruption of the communication between Gallipoli and Varna. The measures prescribed were not executed, and in spite of the insistence of Fauvel before the Marshal de Saint Arnaud, many ships sailing from Gallipoli passed the Bosphorus, and went directly to Varna, where free pratique was accorded them. Cholera then broke out in the army among the newly arrived soldiers and in the hospital. On August 5th the epidemic was violent at Varna, especially among the troops sent into the Dobrudschia. The English army was invaded, having the epidemic on board the fleet. In the Crimea, the epidemic,

helped on by the arrival of the fresh troops, continued until 1856.

The importation of cholera into Constantinople in 1865 equally deserves to be spoken of. Constantinople was in an excellent sanitary condition when the frigate *Mouk-biri-Sourour* arrived from Alexandria, on June 28th, 1865. She had passed more than five days on the voyage, and therefore, in accordance with the rule that then held, free pratique was granted her, the surgeon having declared that there had been no illness during the voyage; but this declaration was false. The evening of June 28th there were landed from this frigate twelve sick persons, of whom one was attacked with cholera, who died during the night, and eleven were affected with cholera. It was learned on the next day that during the journey from the Dardanelles to Constantinople two choleraic bodies had been thrown into the sea. On June 30th nine other cases were landed. The ship was sent into quarantine at the mouth of the Black Sea. The patients were transported to the Marine Hospital, near the arsenal, and here one special circumstance should be noted. The road that went from the landing to the hospital being opposite, it was necessary to carry the sick past the barracks occupied by military workmen in the arsenal, and the first indigenous cases of cholera occurred among these workmen, and on board a corvette that was near their barracks. On July 3d one of these military workers was received at the hospital with a choleraic diarrhoea, and on the 5th presented all the symptoms of cholera. That same day a new case was furnished by the workmen, and another on the corvette spoken of above. The barracks were then vacated, and the workmen were placed in tents on the heights of Okmeidan; nevertheless, the disease continued to rage among them, and among the ships collected before the arsenal, and it attacked on the one hand the guard in the interior of this establishment, and on the other the workmen at the Ministry of Marine, situated very near the barracks of the military workmen. On July 8th two cases occurred outside the arsenal, and from July 10th the epidemic commenced to invade the quarter of Kassim-Pacha, near the arsenal, and inhabited by the workmen of whom we have spoken. It then propagated itself throughout the city.

One more instance of the importation of cholera may be given, as illustrating that a single case, carried a great distance by rail, may give rise to an epidemic.

Toward the end of the month of August, in 1865, cholera suddenly broke out at Altenburg, in Saxony, in the centre of Germany. The first case was that of Lady E—, who had left Odessa on August 16th, and had arrived at Altenburg on the 24th, without having stopped on the journey. She travelled with a child of twenty-one months old, who was affected with diarrhoea. She went to her brother's, and sent for a physician to see her child, whose diarrhoea had become very severe. This woman, who was meanwhile well, said that at her departure from Odessa there had not been in that city any disease; but this was an error, for some cases of cholera imported from Constantinople were already in the hospital in the lazaret, and, the day after the departure of this lady, cholera appeared at Odessa. She said also, that having embarked to go up the Danube, everybody appeared to her to be well on board, although the vessel had passed by certain localities where cholera was raging; however that may be, three days after her arrival at Altenburg, on August 27th, and the very same day that the physician had visited her child, this lady fell ill, and the next day the physician recognized all the symptoms of Asiatic cholera. She died on the 29th. On the same day, in the same house, her sister-in-law was attacked, and died on the 30th. The child died on the 31st. From this house the cholera spread into the city and suburbs. The family of a workman, who died on September 18th at Altenburg, carried the disease to Werdeau, and the house occupied by this family was the point of departure of another epidemic that carried off two per cent. of the entire population of the city.

2. The Transportability of Cholera is Confirmed by the

Results of Restrictive Measures.—We see always that a rigorous sequestration and a rigorous interruption of communication by land or sea, if that be possible, result in preserving certain places or certain countries, and in these facts is a powerful argument against any idea of the transmission of cholera through the air.

In 1867 Messina and the whole of Sicily were entirely free from cholera, and yet vessels coming from infected countries daily passed through the narrow Strait of Messina. And again, during the epidemic of 1856 at Constantinople, the scholars of the Military School, to the number of five hundred, were rigorously sequestered in the establishment, and escaped the cholera that was raging in the neighborhood; and events that occurred at the lazaret of Fort Genoa, in Algeria, in 1884, demonstrated also the efficacy of isolation in order to prevent the transportation of the disease to the neighboring cities.

3. *Transportability as Shown by the General Progress of Epidemics of Cholera.*—If we look at epidemics as a whole, we see that they always follow the course of human currents of travel. It is in the East, or in the countries bordering upon Europe, that we can best follow the development of this law, because in such places the routes are less frequented, and the demonstration is more striking. In order to pass from Persia into Russia in any way except by the great line of travel passing through Erzeroum, Tauris, and Natchischevan, there are only two ways—that over the Caspian Sea, and the land route that follows the western shore of this sea. Both of these routes pass by Recht, Astara, and Lenkoran, and end both of them at Bakou, and in the same way cholera, in the epidemics of 1823, 1830, and 1846, always and invariably passed through Recht, Astara, Lenkoran, and Bakou. At the latter city the land route splits on the north. It continues to follow the western border of the Caspian Sea, and passes by Derbent, and reaches Astrachan exactly as does the sea route, and we have seen cholera at every one of its appearances, in 1823, 1830, and 1846, travel over this same line, passing by Bakou, Derbent, and Astrachan. In 1823 it stopped at Astrachan, while during 1830 and 1846 Astrachan was only one of the steps of its invading march.

The second line of travel passes over the Caucasus. It leaves Bakou, passes by Tiflis, and follows the Caspian Sea to the Black Sea. The point of departure from the Caspian Sea is Bakou. The point of arrival on the Black Sea is Poti, or Trebizond. The epidemics of 1830 and 1846 divided, following both of the two routes that have been spoken of. One current followed the border of the Caspian Sea, another crossed the Caucasus.

This progress of cholera, always following the same lines, is a striking illustration of the law formulated. It always follows the human currents, in the steps of the traveller. It is imported by man alone, and precisely the same point is shown if we follow the successive steps of the epidemics that have travelled by the sea route.

As an illustration, the epidemic of 1854 in the Crimea was due to vessels coming from Marseilles, and carrying troops from an infected country. Cholera appeared successively at every one of the points where these vessels touched. They landed at Messina, and Sicily was invaded. They touched at the Piræus, and Greece was attacked. They stopped at Gallipoli, and cholera appeared at Gallipoli. Constant communication was being held between Gallipoli and the Dardanelles, Constantinople, and Varna. Cholera developed at all three places. The same was shown in the progress of the epidemic of 1865. It must not be supposed, however, that the assertion is made that cholera took the special direction from east to west; on the contrary, it radiated from India in all directions—north, south, east, and west—according to the ease and number of the means of communication.

4. *Transportability as Indicated by the Evolution of Epidemics in Infected Localities.*—Many examples of this may be quoted, among which are the following:

In Constantinople it is possible to trace out the successive extension of the disease up to the time of its general diffusion. At Constantinople it manifested itself first at

the arsenal, where it had been carried by the sick who were landed from the ship *Moukbi-Sourour*. From the arsenal it reached the neighboring quarter of Kassin-Pacha, and then a few cases appeared in different parts of the city, for the most part of persons who had fled from the quarter first attacked. Up to July 16th the total of the deaths from cholera in the entire city, except those at the Marine Hospital, reached one hundred and thirty, when suddenly it was learned that the disease had broken out with violence at Eni-Keni, a village situated on the Bosphorus, twelve or fifteen kilometres from the quarter where the epidemic had begun. It was established that the first case of cholera had appeared on July 11th, in a Turkish café, in a workman coming from Kassin-Pacha; that on the next day many of the individuals who frequented this café fell ill, and two died; that during the following days the disease was propagated in the quarter until the 16th, when, after the occurrence of several deaths among prominent families, a panic seized the whole population of the village, who fled in all directions. Mussulmans, Greeks, Armenians, and Jews fled into other villages and other quarters of the city which were then unaffected, but in which the cholera speedily made its appearance. The Jews in particular, who had been the most seriously attacked, and who carried with them their soiled clothing and their dead, became the special propagating agents of the disease. At Kous-toundjouc, at Kas-Keni, and at Balata, the epidemic broke out immediately after the arrival of these fugitives. From this moment dates the generalization of the epidemic. It is not necessary to add other examples. The same thing is shown in the history of every local epidemic that has been intelligently traced.

It has been opposed to this idea of the transportability of cholera that sometimes a restricted intercourse has failed to arrest the progress of the disease; but in all these cases the measures were either tardily employed or applied without scientific rule. Others have spoken of the immunity of countries which had not protected themselves by any sanitary measures. The answer to this is the question, whether cholera, although it is a disease capable of spreading by infection, must, therefore, be possessed of a method of forcing this infection. And, in conclusion, no matter what the differences of opinion are, the law of transportability remains absolutely established by all the facts yet obtained in regard to cholera.

Methods of Transportation of Cholera.—In a consideration of the question of the method of transportation of cholera, we are to look at two principal points, the agent of cholera, that is, the organism of the disease, and second, the medium.

The agent of cholera is unquestionably a bacterium, having India for its origin. It extends itself, and reproduces itself indefinitely, and many media serve as vehicles for its transportation throughout the entire world, but this choleraic agent would be wholly powerless if it did not encounter favorable conditions for its development. The medium, therefore, is indispensable to its power, and this favorable medium is made up of certain telluric conditions, the surroundings, and so on. So far as the methods of transportation of cholera are concerned, therefore, we have to consider more the medium in which it appears than the cause of the disease itself. Fauvel has expressed this truth as follows: "That a fire is not proportionate to the spark which gives it birth, but to the combustibility and mass of the material that it encounters." So, frequently, a few cases, or one only, as at Altenburg, are sufficient to produce the explosion of an epidemic.

The clinical consideration of the means of transportation of cholera is to be made under the following headings:

First, the transportation by men attacked by cholera, and the rôle played by the closets that have received choleraic excreta. A person arriving from an infected place is always necessary for the beginning of an epidemic. In other words, man himself is the most powerful agent for the spread of cholera, the specific micro-

organism being found, as has been demonstrated by innumerable experiments, in the excreta. Washerwomen have been attacked by the disease after washing linen soiled by evacuations, while others, who had simply touched this linen, also contracted the malady. Budd relates (quoted by Hirsch in *Schmidt's Jahrbücher*, vol. xcii., p. 255) that in 1854 a person affected with cholera arrived in an English factory of six hundred and forty-five workpeople. There followed one hundred and forty-four deaths from cholera in five weeks. The disease developed solely among those who made use of the closets where choleraic dejecta were deposited. Instances of this kind can be multiplied almost indefinitely.

Second, the transportation by means of choleraic diarrhoea. As illustrations of this, innumerable instances might be quoted, especially that mentioned by Budd in the reference given above. A person sick of diarrhoea came into the midst of a perfectly healthy population in a colliery, and died. Diarrhoea became general, and seventeen persons contracted cholera. The case of Dr. Alexander, in the *Gazette Médicale* for 1849, is also an illustration of this point. There was not at Hamel, a village twenty-five kilometres from Amiens, any indication of cholera, when, on April 4th, from Paris, where cholera existed, there arrived a soldier sick with diarrhoea. He was received into his parents' house where he remained three days. On the 14th he went to the Hôtel Dieu, and the same day his brother, who had come a number of times to see him, was attacked by foudroyant cholera and died in twelve hours. His wife died three days afterward. The father, who had shown some symptoms of cholera, was attacked with cholera on the 11th, and died on the 15th. Another son of this man, seventeen years old, and a child of four years, his grandson, were attacked with cholera and got well. The father-in-law of the brother who had taken care of him and his daughter were attacked by cholera, but recovered. A child of eleven years, who was often at the house and whose parents had taken care of the same brother and his wife, was attacked on the 14th and died the following day.

Third, Can the bodies of persons dead of cholera communicate the disease? Although the evidence seems to point toward this being a possible danger, it is not a serious one in civilized countries.

Fourth, Can cholera be transported by healthy individuals? This must be answered in the negative. The facts quoted that seem to show that this may occur, must be explained by supposing that the individuals who were believed to be entirely well were in reality sick of a choleraic diarrhoea, or else that they carried clothing or linen soiled with choleraic material. The studies of cholera during 1892-93 in Europe have shown that the cholera vibrios may be present in the dejecta of people apparently healthy, with well-formed stools, as well as in those who are suffering from a mild diarrhoea without other notable symptoms. These vibrios were virulent and presumably capable of inducing severe cholera in more susceptible individuals.

Fifth, Can cholera be transported by living animals? Animals are not susceptible to the disease. A certain number of experiments have succeeded in producing cholera in animals, but with great difficulty. There is no fact to support the supposition that animals can carry the disease, either on the skin or in the hair.

Sixth, the transportation of cholera by means of clothing, personal effects, and so on. The disease cannot be so transported unless these materials have been contaminated by cholera dejecta. This, of course, is an exceedingly important point, for if soiled, the material may be dangerous; if it is not soiled, there is no danger at all, even if it comes from cholera centres. It is of equal importance to know whether contaminated objects have been packed up or exposed to the air. A contaminated object exposed to free air for a definite time loses its power of transporting the virus. The conference of Constantinople considered that a very short time was sufficient to do away with all danger, and recent bacteriological research

has wholly confirmed this opinion. On the other hand, contaminated objects that have been packed up and kept shut out from the air retain their virulence for a greater or less length of time, as may be shown by many instances.

Seventh, Can cholera be transported by merchandise? Although merchandise imported from India, whether to Suez or directly to Europe, has never been known to transmit cholera, this method of transportation is not absolutely impossible, and many of the materials brought from India—cloths, and so on—retain in their interstices a confined air that certainly might preserve and transport for a great distance the contagion with which they may be impregnated; but although this is a possibility, it is not probable, and the conference of Constantinople unanimously accepted the absence of proofs of the transportation of cholera by merchandise, while it admitted the possibility of its being done, under certain conditions. Since that time, Zehnder, the Swiss delegate to the Vienna Conference, in 1874, cited facts in favor of the danger of rags in transporting contagion (see the report of the International Sanitary Conference of 1874, page 273). But at the conference in Rome, in 1885, Koch disputed the interpretation that had been put upon these facts.

Eighth, water is perhaps the most important agent in the spread of cholera, and evidence to this effect was obtained long before the discovery of the cholera spirilla. J. Simon brought out some facts in England which confirm this statement. At London thirteen deaths out of a thousand inhabitants occurred among those whose houses were supplied with river water in the neighborhood of the sewer. Tested at this point, the water yielded forty-six grains of solid residue to the gallon. In other houses in the city that were in the same hygienic condition, but not supplied with this water, the mortality was only three and seven-tenths in a thousand, but the water which they used had been taken from outside the city, and yielded only thirteen grains of solid residue to the gallon.

It is not improbable that the cholera vibrio can live longer in a pure water than in one containing large numbers of other micro-organisms. It has remained viable for eight hundred and seventy-eight days in a sterilized pond water, which for at least three hundred and five days contained other bacteria. During this period they retained their usual susceptibility to heat and desiccation, showing that a true spore formation of the usual kind is not necessary for prolonged viability in this species.

At Halle, Delbruck noticed that in the prison, where the epidemic had developed very largely, the wells communicated with the drains. At Brachstedt the epidemic arrested itself just as soon as a suspected well was closed. Delbruck explained the less intensity of the epidemic of 1867, compared with that of 1866, by the fact that the carrying of the water had been modified. Water was furnished almost pure in 1867, while up to the autumn of 1866 the conduits carried the water from the Saale through a region where all the discharges of the city were scattered. Ballot also spoke of the influence of impure water on the spread of cholera in Holland. Snow, in England, and innumerable other writers in Europe, India, and America, lay the greatest possible stress upon impure water as the special means for the conveyance of the infective agent of cholera. (See the article on *Water*, in the present volume.)

The contamination of water played an extremely important part in the extension of cholera in Egypt in the epidemic of 1883. The Mussulman population of Egypt bathe very frequently, but they are not careful about the water that they use for drinking. At Damietta the water is exceedingly foul upon the points of the Nile from which the water-carriers fill their water-casks, and just at these places are the special spots selected for bathing. The houses along the bank discharge their foul material directly into the river, and drains carry to it discharges from other houses, and from the mosques. According to Koch, these mosques play an extremely important rôle in the spread of cholera. The German cholera commis-

sion was able at Damietta to examine a number of mosques, the description of the arrangement of which is as follows: Only that part of the mosque that is directed toward Mecca is used for prayers. At the other end is an open space, in the centre of which is a tank for bathing, and sometimes this water remains several weeks without being changed, and surrounding the basin are a series of urinals and closets. The discharges from the whole are passed into the Nile, so that it is not strange that the infected material should be transported by such a water supply.

In the "tank districts" of India the conditions appear particularly favorable for the propagation of cholera from the sick to the well. In these districts cholera is very prevalent. The region is low and the land upon which the dwellings are situated is made ground derived from the immediate neighborhood, leaving pools which constitute the "tanks." The drainage from the dwellings flows into these relatively or entirely stagnant bodies of water, which is also used for bathing and, in many cases, for drinking purposes.

The epidemic of 1884 furnished new proofs in favor of the spread of cholera through the agency of water. Messrs. Marey, Brouardel, and Thoinot especially insisted upon this point. Marey, at the sitting of the Academy of Medicine, October 14th, 1884, said: "Among the influences that can cause the spread of typhoid fever or cholera there is one that by its intensity dominates all the others—that is the contamination of public water supplies." If a number of epidemics of cholera be studied, it can be determined, in effect, that cholera easily follows watercourses; that it is especially along small watercourses that it is propagated, is most frequent and striking. In order to explain this, there are but two hypotheses that are possible.

First, brooks, torrents, or rivers flow in valleys that are often narrow and shut in, and the villages found there often can have no communication except with each other. When one is attacked, it is a perfectly simple matter that the others should be also in their turn. This explanation is very plausible; for certain cases, and some epidemics, can be explained in no other way. The great rivers, the large watercourses, along which are scattered regions attacked by cholera, serve for the propagation of this disease, like the great roads of travel, in this way only, that they are lines of communication frequented by travellers.

Second, water is certainly a propagating agent of cholera. It is the water of a torrent, a brook, or a small river, contaminated in one part of its course, that transports the disease to the inhabitants on its borders that drink of the water, and innumerable instances can be brought forward to illustrate this point also.

Proust (*loc. cit.*, p. 216) speaks of the choleraic agent having for its vehicle of transportation either the air or the water, but the evidence in favor of the air as one of the transporting agents of cholera is nothing, and the weight of scientific evidence of late years militates against such a means of transportation. Altitude seems to have but slight influence upon the development of the disease up to a certain point, although Farr (in the Registrar-General's Report on the Mortality of Cholera in England, London, 1852) has attempted to demonstrate that the mortality from cholera was in inverse proportion to the elevation. The objection to this is, that the less frequent occurrence of cholera on the most elevated points may be due to the fact that the less accessible points are more thinly inhabited.

Moisture, taken in connection with the subsoil water, is a favoring cause of the greatest importance, and observations in this direction have furnished the basis for Pettenkofer's theory of the connection of subsoil moisture with cholera.

The development of the epidemics of 1836 and of 1854 seemed to coincide with the period of greatest diminution of the subsoil moisture in Munich, and therefore the choleraic contagion with which the soil is impregnated appears to disengage itself more easily. Hirsch reached

a similar conclusion. Kreuzer, in 1855, at Vienna, and again Pettenkofer, at Munich, observed the same facts. Pettenkofer's theory differs from others, in that, putting aside the chemical composition of the earth, he attaches a special importance to its physical characteristics, its density, its porousness, etc. He considers that the condition of the subsoil of localities and of houses plays a rôle of special importance in the propagation of cholera, and upon this special cause he places the development of an epidemic, after an importation from without; and, studying almost exclusively the physical condition of the region, the compact or porous condition of the subsoil, he considers that not only the primitive earth, and the soils of the transition period, but also the secondary formations, produce immunity when they are exposed to air in the condition of rocks. On the other hand, every porous soil that is susceptible of imbibition can become easily impregnated with fluid, or with gas, and vegetable earths as well as silicious earths may form "fat," always moist, lands, throwing out continual moisture about them, favoring the diffusion of the germs of cholera. Where the soil is made up of a compact calcareous rock cholera never becomes epidemic, and a few cases observed in such situations as the result of importation, do not propagate the disease.

Pettenkofer's theory has two points that must be distinguished from each other.

First, the nature of the soil. The soil must be porous, easily permeable, and also easily impregnated by liquids and gas. This condition is a permanent one.

Second, the level of the subsoil moisture. This level being movable, the effect is variable; when subterranean waters have reached the maximum of their elevation, there is neither decomposition of organic materials nor throwing off of miasms. If the subsoil moisture descends to a lower level putrefaction begins, the miasmatic vapors are thrown off more intensely, and just at this time the epidemic reaches its greatest development. This second point of his theory, certainly an ingenious explanation of certain cases, appears to be much more hypothetical than the first, the question of the porosity of the earth.

To sum up, Pettenkofer's theory, while it scarcely has the value ascribed to it by him, certainly seems to afford a partial explanation of the propagation of cholera by means of the porosity and moisture of the earth.

Ninth, atmospheric conditions play a not very important rôle, although the influence of season is manifest, and, apparently, storms sometimes seem to aggravate considerably an epidemic.

Somatic Conditions.—Race or nationality has no influence upon the development of cholera. The special influences favoring it are those of misery, fatigue, cold, and depressing mental conditions, which, by diminishing the resisting power of the body, render it more susceptible to the influence of the epidemic. Collections of human beings, in other words, agglomeration, play a very considerable rôle in the propagation of epidemics; so also do methods of transportation. Railroads are often the means of propagation, as was the case in the instance of Altenburg, quoted above. The epidemic of 1865, in Paris, was started by a woman who left Marseilles, with a choleraic diarrhoea, and was attacked with cholera upon her arrival in Paris. Transportation by caravans does not give much chance for the spread of the disease, when the distance passed over is of great extent; in fact, a great desert is the best of all obstacles to the propagation of cholera. In ships are most often found united the conditions of crowding and confinement favorable for the development of the choleraic agent.

Proust appears to believe that these elements do not have much potency if the entire ship's company come from the same infected region—in other words, have acquired an immunity in a choleraic focus; but if the ship's company has received a partial renewal, if new persons have come on board among the acclimated passengers, cholera finds a new favorable medium for attack, and, if aiding circumstances appear, the ship may become the centre of an intense epidemic. He goes on to speak of

this "law of accustoming," in what takes place in armies, the great fairs, and the pilgrimages; for when cholera is carried into these great collections, if the mass of people have not undergone the "choleraic acclimating," the explosion of the disease is rapid and the mortality considerable, but only continues for a few days, and ceases soon. The Crimean War furnishes an example of the rapidity of development and intensity of the disease among vessels free from the choleraic influence.

At the commencement of April, 1855, there reached Constantinople from France, fifteen to twenty thousand troops, made up in part of the Imperial Guard. These troops had not, during their voyage, a single case of cholera among them. They camped on the heights of Masslak, in an extremely healthy situation, and at that time there were in the city of Constantinople but very few traces of cholera. The rolls of the French military hospitals gave only fifty-three cases during March, and the roll of April 11th showed none. In the Crimea the cases of cholera were also very few, and nevertheless the troops were hardly settled at Masslak when, on the night of April 14th and 15th, cholera broke out among them, and a severe epidemic followed.

Fauvel ("Memoire lu à l'Acad. des Sciences," Paris, 1883) sums up this question of immunity in the following propositions:

"1. The ports of India that are the seat of endemic cholera are never the scene of a great epidemic.

"2. This fact relates to the general, but not absolute, immunity enjoyed by the native population of these parts.

"3. This immunity does not exist in the endemic localities for strangers who are in a condition favorable for contracting the disease. These are especially the Musulman pilgrims who come to Bombay to embark for Mecca.

"4. The epidemics of cholera that develop in India, in the regions where the disease is not endemic, come from the places where it is endemic, and are favorable for attacking the Hindoo pilgrimages.

"5. The epidemics observed among the pilgrims to Mecca can also be traced to the localities where cholera is endemic.

"6. A severe epidemic of cholera confers upon the country or upon the locality which it has attacked a more or less complete immunity, which is more or less durable, and of which it is impossible to formulate the law for Europe, but which in India appears to last for a number of years.

"7. In the Hedjaz, and in the sparsely populated parts of Arabia, cholera has but a feeble tendency to propagate itself among the native population.

"8. The fact of the existence of a great epidemic of cholera in any country whatever is a proof that cholera is not there endemic."

To sum up, new scientific facts bear upon the question of immunity and make them clear upon a side hitherto unknown. The etiology and prophylaxis, in especial, of cholera receive from these facts new indications, and these facts also appear to be the expression of a law that includes an entirely different category of infectious diseases, which leave after them an immunity of a greater or less extent.

Period of Incubation.—The question of the period of incubation of cholera gives rise to a great deal of discussion. It appears, however, that in the immense majority of cases a period of a few days is sufficient for the incubation, and that sometimes this may require only a few hours. This fact is easy to observe if the beginning of the disease in a city or upon a ship be studied.

The Cholera Conference at Constantinople concluded as follows: "That all the facts cited in regard to a period of incubation longer than a few days are based upon cases that are not conclusive, either because the premonitory diarrhoea was comprised in the period of incubation, or because the infection could have occurred after the departure from the infected locality." The following is an instance:

On November 3d, 1848, upon the ship *Swanton* there were two hundred and eighty-nine emigrants for New Orleans, and the cholera did not break out on board until November 25th—that is to say, the twenty-third day of the voyage—and occasioned thirteen deaths. A certain number of these emigrants came from points in Germany where the cholera existed. This long period of incubation can be explained upon two hypotheses: either the passengers had with them clothing soiled with choleraic materials, which, placed in a confined air, could transmit cholera; or certain of the individuals embarked might have been affected at the time of their embarkation with a diarrhoea that might later have developed into true cholera. The duration of this premonitory diarrhoea has been much discussed, and in general it has been concluded that it does not last more than three days, and when it does pass this period, it is rarely prolonged beyond a week, and that therefore an individual isolated from all sources of contamination, and in whom the diarrhoea should be prolonged more than eight days after this isolation without presenting any characteristics of cholera, could be considered non-choleraic. But Griesinger among others dissents from this opinion, and declares that the period of incubation of cholera may be much longer. A bacteriological examination furnishes the only method of settling the question.

The experience of those who carefully studied the epidemic in Hamburg in 1892-93 points to an incubation of not less than twenty-four hours. After this period there may be a diarrhoea which attracts little attention, but which is in reality the first stage of the disease. In other cases the onset of symptoms may be very sudden, leading to collapse and death within a few hours. It has been noted that in the early days of an epidemic the spirillum develops more slowly in artificial media than is the case later in the course of the epidemic.

DESCRIPTION OF THE DISEASE.—The clinical manifestations associated with the presence of the cholera vibrio in the intestinal contents are so various that it is impossible to give a single clinical picture of Asiatic cholera. During epidemics of the disease this micro-organism has frequently been isolated from the feces of people presenting no evidence of any disturbance in health. In other cases its presence is associated with symptoms of the most marked character, followed by a speedily fatal issue. These facts by no means throw doubt upon the etiological significance of the cholera vibrio; for similar observations are well known in other infectious diseases, such as diphtheria, typhoid fever, and even infections with pyogenic micro-organisms.

Cases in which the cholera vibrio is present in the digestive tract without being associated with symptoms are of great sanitary importance, because this very absence of all manifestations of disease renders the spread of the infection from place to place very difficult of control or detection. It is also important to the individual himself. There are cases on record in which people in apparently perfect health have left regions where cholera was epidemic, have remained for a time free of any signs of ill health, and then, as the result of some dietary indiscretion, have suddenly succumbed to an attack of severe cholera, with the vibrios in the alvine discharges. It appears evident that in such cases the cholera vibrios in the intestine are virulent, but that the resistance of the individual was so great as to prevent the usual effects of infection until some additional factor created a susceptibility. It is not possible to state the frequency of such latent infections in times of epidemic cholera, but where the spread of the disease takes place through a contaminated water supply it is reasonable to suppose that they must be more frequent than could be indicated by any statistics as yet in existence. Rumpf, in his studies of the epidemic in Hamburg in 1892-93, reports that cholera vibrios were found in the feces of 62 individuals during the small after-epidemic of 1893, and that of these 19 failed to show signs of any great constitutional disturbance. These cases were studied because they had been closely associated with cases of pronounced cholera in the

city or upon vessels in the port. On the other hand, between February 23d and June 1st, 1893, 70 cases of diarrhoea were investigated to learn of the presence of cholera vibrios in the discharges, with negative results.

Leaving out of further consideration these important latent infections, we may divide cases of cholera into three groups, according to the severity of the clinical manifestations: First, choleraic diarrhoea, in which the symptoms present little beyond a marked looseness of the bowels; second, choleric, characterized by vomiting and considerable constitutional disturbance as well as diarrhoea with rice-water discharges; and, third, algid or asphyctic cholera or cholera gravis, which has hitherto served as the type of the disease.

These terms are not used to denote nosological entities, but merely to furnish concise expressions for clinical differences dependent upon variations in the relations between the virulence of the infection and the susceptibility of the patient. In individual cases the less severe forms of the disease may pass into the graver types, where conditions arise which modify these relations. In many epidemics the milder types occur most frequently early in the history of the epidemic, to be succeeded by a larger percentage of severe cases at the height of the epidemic, which are in turn followed by a preponderance of the milder cases as the epidemic draws to a close. These clinical observations harmonize with the experience that cultures in artificial media grow less rapidly early and late in an epidemic than at its height.

Choleraic Diarrhoea.—In the milder cases the stools are feculent or bile-stained and watery, are unaccompanied by much pain, and differ considerably in frequency in different cases. The symptoms usually first appear at night and are accompanied by some flatulence. The general health may remain good. In severer cases the stools are more numerous; the appetite is lost; the tongue becomes coated, and there is a feeling of gastric depression. The amount of urine is decreased. The patient becomes restless and suffers from headache. Dragging pains in the calves may be troublesome. These symptoms last a few days, and in favorable cases then subside. The course of the affection depends largely upon collateral circumstances. Indiscretions in diet, over-fatigue or imprudence of any kind exert an unfavorable influence upon the patient, and in many cases this choleraic diarrhoea passes into the severer forms of cholera. Although the cholera vibrios are regularly found in the discharges, the latter do not acquire the rice-water character typical of the severer forms of the disease.

The affection may prove fatal in people of diminished resistance; in the young or aged death being the result of exhaustion; but recovery is the rule.

Choleric.—Sometimes this type of cholera is preceded by the form just described, but more often the first symptoms noted are general malaise, loss of appetite, and nausea. The stools then become more frequent. They are at first feculent, but soon become more liquid and then assume the "rice-water" character of those in severer cases of cholera. These discharges consist of a serous fluid, rendered turbid by large quantities of desquamated intestinal epithelia, and frequently tinged more or less pinkish by red blood corpuscles. When examined microscopically the spirilla may frequently be seen in great numbers, but in many cases they cannot be made out as such, but appear as granules of various shapes. In addition to the symptoms mentioned above, vomiting comes on early in this form of the disease. After the stomach is emptied of food, the vomitus is a thin fluid containing some bile, or it may be colorless. Pain in the epigastrium, headache, and thirst appear as the disease progresses. The quantity of urine is reduced and albuminuria appears. The skin is cool and the volume of the pulse diminished.

Choleric may pass into algid cholera, or the symptoms may gradually subside and recovery follow; but not infrequently convalescence is delayed by a long period of debility and mental hebetude, resembling the typhoidal stage of algid cholera.

Cholera Gravis; Algid or Asphyctic Cholera.—In this form, which has usually been regarded as the typical manifestation of the disease, the attack may suddenly develop, its onset being marked by great uneasiness, repeated discharges from the bowels, followed by syncope. This attack may overtake the victim while walking on the street in apparently good health. It is often preceded by a state of vague suffering, rapid prostration, deep colicky pains, anorexia, sometimes a diarrhœa, profuse sweats, disturbance of the senses, and more or less retardation of the pulse. After the development of the disease the symptoms follow each other in such a way as to allow of a division into two distinct periods.

First Period.—This is marked by an increase in the number of dejections and acts of vomiting; a flux is established which is at first serous or slightly bilious, and afterward becomes "choleraic." This term is used to designate those characteristic discharges of cholera which are liquid, whitish, grumous, sometimes resembling unclarified whey, sometimes a decoction of rice or oatmeal, and sometimes thickened meal, and nearly clear, which emit an insipid spermatic odor, and sometimes present traces of blood or bile. These evacuations are rarely absent, often continuing to the termination of the disease. Burning thirst, pain in the epigastrium, and prolonged hiccough are usual accompaniments. Intense cramps of the limbs occur, particularly in the calves of the legs; the muscles are often in a state of tonic contraction. Spasmodic movements, as involuntary flexion and extension of the fingers and toes, may often be seen. The pulse is very feeble, often imperceptible. The features are altered, trembling and great agitation come on, the pulse becomes suppressed; bluish spots appear, first upon the extremities; the skin becomes blue or black almost everywhere; the nails are livid and almost black, the fingers wrinkled, and the genital organs retracted. The volume of the body diminishes rapidly and perceptibly; the eyes sink in and are dull, with a bluish circle surrounding them; the conjunctiva fades, respiration is slow and feeble, the breath cold, and the pulse is reduced to a mere oscillation. The secretions are arrested, especially the urine, the voice is reduced to a whisper, the nose is cold and—rarely—gangrenous, the cornea is flattened and puckered; spots of blood appear on the sclerotic, viscid sweat on the face and limbs; the intellect becomes obscured, respiration is embarrassed, hiccough commences, and death follows, in the midst of an apparent calm. This is called the *cold, livid, or asphyctic* period. When patients escape death in this stage they enter upon the

Second Period.—In this the coldness ceases to increase, warmth returns, the pulse improves and gradually becomes febrile, the face regains color, the eye becomes animated, and a general reaction occurs.

If recovery is to be easy and rapid, vomiting becomes less frequent, the diarrhœa remains, but the discharges no longer present the appearance peculiar to the disease; the secretion of urine returns, nausea, thirst, and pains in the stomach cease to be felt, the pulse becomes regular, and convalescence begins.

If reaction is incomplete, the cold stage returns with renewed severity, or, on the other hand, if reaction be too severe, such accidents may occur as apoplexies, spasms, convulsions, local congestions and inflammations, and occasionally latent pneumonia. Stupor is sometimes present, with some of the signs of the last stage of typhoid fever. Swelling of the parotid glands and various skin affections, as roseola, urticaria, erythema, erysipelas, etc., may appear toward the close of the disease.

The average duration is from one to three days, but sometimes death occurs in less than six hours, and is occasionally delayed a long time—in one case for fifty days.

Complications and Secondary Affections.—Complications are rare, and apparently accidental, but secondary affections, either direct results of the cholera or due to increased susceptibility to infection or to debility, are common.

Course, Duration, and Termination.—If death does not

occur during the algid stage, a peculiar transformation in the disease takes place and *reaction* sets in. This reaction varies in different cases, being slow and tedious in some, and abrupt and rapid in others; its course is not essentially modified by any antecedent disease, even those occurring as complications.

In the vast majority of cases cholera runs its course with great rapidity, the greater number of attacks lasting from eighteen to twenty-four hours, the shortest from one to six hours, and the longest from fifteen to twenty days. Its duration is the shortest at the height of an epidemic.

The termination of epidemic cholera may be favorable, the progress of recovery varying widely in different cases; it may be complete in a few hours even, and the patient may return to his ordinary occupation; on the other hand, it may be delayed until after a long and perilous struggle against complications and secondary affections. There may remain a general debility such as is not often seen after any other disease; the emaciated features, languishing expression, capricious appetite, obstinate gastralgia, colic, wakefulness, tendency to coldness, partial or general, and intellectual and moral dejection persist for a long time. An attack has been known to change the whole constitution and temperament of a patient. One attack appears to furnish no immunity against another, and relapses are always to be feared.

SYMPTOMS IN DETAIL.—Besides this general account of the disease the symptoms should be briefly discussed in the order of their occurrence.

Precursory Phenomena.—An attack is often preceded by initiatory uneasiness, which should attract attention; such are languor, pallor, anxious expression, sunken features, weight in the stomach, and movements of the intestines. Then vertigo follows, with abdominal pain, dimness of vision, and difficulty of hearing; the eyes become more brilliant than ordinary, like those of a drunken man. Sometimes circulatory disturbances are the first phenomena of the disease, marked by bluish circles around the eyes. In other cases, the progress of the preliminary symptoms differs—there are diminution of appetite for several days, general disagreeable sensations, and frequent alvine dejections, without pain, which are yellowish, more and more fluid, and, finally, become almost like water. A diarrhœa like this may occur without any other symptoms and develop into a severe case of cholera. Lastly, the disease may come on suddenly, and without warning overwhelm the victim with its full force—this often occurring at night.

Diarrhœa.—This is most frequently the mark of the onset of the disease, and when it is so, the stools become at once more and more frequent. Fifteen, twenty, or more dejections in twenty-four hours are usual, and in some cases (these are fatal) the evacuations occur in an almost continuous and involuntary jet. They are often accompanied by colic, borborygmi, and gurgling, either spontaneous or excited by pressure upon the abdomen. They are at first made up of bilious, fecal, or sero-mucous matter, but soon assume the characteristic appearance, viz., that of a whitish flocculent fluid such as has already been described. A large flocculent sediment is deposited from this fluid, a part of it looking remarkably like cooked rice. The fluid is blood-serum, and the sediment is made up of the epithelial lining of the intestines and of mucus. Sometimes the evacuations are tinged with blood-coloring matter, giving them the appearance of the lees of wine, or they may be of a deep brownish color from the same cause. The frequency of the dejections is not always increased with the progress of the disease, they are occasionally completely arrested during the cold period, and death may occur without their beginning again; on the other hand, they may return with increased violence. In those cases in which the acute attack is followed by a prolonged period of depression, during which the patient presents the typhoid state, the choleraic discharges give place to loose, diarrhœal evacuations having a fecal odor. These may be frequent and persist for a number of days, gradually diminishing as convalescence advances;

but the typhoid condition is always favorable to the development of dangerous complications, and cases of cholera which take this form are by no means favorable. The abundance of the renal secretion is considered a valuable prognostic sign. After recovery obstinate constipation may occur.

Vomiting.—Nausea and vomiting, sometimes almost constant, occur from the very beginning of the disease. The vomitus is poured out by an almost constant effort; it does not differ in character from the dejecta, except that it is sometimes more limpid, and is sometimes slightly tinged with bile. It is very rare that vomiting persists to the second period of the disease, but the ingestion of the smallest quantity of fluid may excite it with great violence. It often alternates or coincides with a very troublesome hicough.

Abdominal Pain.—This often precedes the vomiting and choleraic diarrhoea. It is griping, and of the most intense character, situated in the region of the epigastrium, or over the entire abdomen. A doughy sensation is communicated to the hand upon pressure, and percussion gives, usually, an almost universal dull or flat note.

Anorexia; Thirst; Tongue.—Loss of appetite is complete, and corresponds in point of time with a burning and inextinguishable thirst. The throat and mouth are parched, the tongue is frequently clean, commonly large, pale, moist, cold, very rarely dry, and occasionally covered with a yellowish coat. This condition is peculiar to the first period; it varies, later on, with the degree of reaction, or with the nature of the complications and secondary affections.

Urine.—Upon the first appearance of the gastro-intestinal evacuations the urine becomes scanty, and is frequently completely suppressed; exceptional cases are reported in which it remains normal throughout. Emission is involuntary. Sometimes, after suppression, it reappears about the middle of the cold stage; being again suppressed for the remainder of the disease. The desire to urinate remains, although the power may be lost; the secretion and flow are generally re-established during the period of reaction. There are no observations pointing to the occurrence of renal disease. The urine is especially rich in indican and other ethereal sulphates. Ammonium salts are also increased and aceto-acetic acid may be present in considerable quantities. These changes in the urine are attributable to the ready absorption of putrefactive products from the intestinal contents, due in part at least to the loss of the epithelial lining of the bowel, and to the reduction of oxidative processes within the body.

Cramps.—Violent and prolonged cramps, beginning with the first diarrhoea, in the muscles of the legs and extending to the abdomen, arms, and even to the face, are among the most characteristic, and at the same time the most terrible, symptoms of cholera. They sometimes persist throughout an attack, and even after a cure, and muscular contractions have even been observed after life was extinct. During an epidemic cramps have been observed without any other symptoms. It has been suggested (Weir Mitchell: "Injuries of Nerves," p. 52, ed. 1872) that they are caused by the loss of water from the body, and the consequent "drying" and irritability of the nervous system, a phenomenon analogous to the violent contractions of a frog's leg when the sciatic nerve is exposed and allowed to dry in the air.

Headache; Derangement of the Senses.—Weight in the head, with giddiness and vertigo, occurs during the invasion; cephalalgia, often very severe, appears during reaction; it is generally heavy, and more marked in the frontal regions; at the same time occur ringing and buzzing in the ears. The sight is generally affected during the whole course of the disease; it is blurred, double, or perverted, so that the patient sees objects colored blue, or alternately black and red; it is occasionally completely extinct. The touch and general sensibility are much blunted.

Intellectual Faculties.—These are generally unaltered, although the power of expression may be impaired. It

is only in certain modes of reaction in the second stage, and in certain complications, that stupor and, more rarely, delirium occur.

Strength.—There is in all cases almost entire loss of strength, the least displacement of the limbs being unbearable. Most patients, either stretched on the back or with the limbs closely drawn up, remain in a state of complete immobility through fear of fatigue. Transient faintness appears in some cases.

Voice.—It is characteristic; changing very rapidly from a state of feebleness at the commencement of the disease to a rough and whistling tone. It occasionally becomes entirely extinct, but in some cases retains strength enough for loud cries. It gradually returns to its normal condition as the disease lessens in intensity and recovery progresses.

Respiration is ordinarily very difficult, the frequency varying from ten to fifty-two per minute. This does not depend upon any altered condition of the lungs as revealed by physical examination, but seems to be in some way connected with the presence of less than the normal amount of carbonic acid in the expired air.

Circulation.—The circulation is very gravely affected. The pulse becomes more and more feeble, and disappears entirely at the height of the cold period; it is always more frequent than in health. The blood moves slowly and will not flow from a vein or an artery of small size. This sort of stagnation aids in producing the bluish hue peculiar to the cold stage. This bluish hue makes its appearance first in the extremities, in the genital organs, and in the face. It is especially observable in patients who are plethoric and of florid complexion. It diminishes and often disappears during reaction, and sometimes does not occur at all. It may go so far as to produce gangrene, as has been observed in the nose, tongue, and sexual organs.

Temperature.—The temperature is seemingly reduced; the expired air being only 25° to 27° C. (77° to 80.6° F.). This reduction in temperature is confined to the surface, however, the internal temperature being higher than in the highest fever (Guterbock, *Virch. Arch.*, xxxviii., p. 30).

Appearance.—The aspect is characteristic; the face is contracted, the brow wrinkled, the cheeks are hollow, the lips thin and pressed in upon the teeth, the complexion becomes livid and bluish, the eyes more and more sunken, and surrounded by a dark circle. Expression is lost by degrees, and death seems to have occurred while life is still present. The eye is dim, its surface wrinkled, sunken, and sometimes dry, the globe is left exposed by the lids, and the conjunctiva becomes injected and covered with spots of blood. Even if recovery takes place, the normal aspect of the face returns very slowly.

COMPLICATIONS, SECONDARY AFFECTIONS.—*Complications* are rare and apparently accidental; among them peritonitis, jaundice, gangrene, oedema of the lungs, erysipelas of the face, abscesses, ulceration of the eyelids, and aphthæ may be mentioned as of occasional occurrence.

Secondary affections are, however, very common. They may consist of gastro-intestinal inflammations, immediate, or after some days of convalescence, or of affections of the respiratory organs. In other cases persons who have apparently escaped the accidents of cholera have a secondary fever, described as of a typhoidal type, dry skin, tension and tenderness in the epigastrium, jactitation, dry tongue, bilious stools, and chills. Various skin eruptions occur, and temporary albuminuria has been observed following an attack of cholera. The most grave of the secondary affections, however, are those which affect the nervous system. The cerebral congestions during reaction are, in some cases, followed by a typical meningitis with trismus. Rayer's "État cérébral cholérique" includes a group of phenomena distinct from those of meningitis, which supervenes upon the cold stage; the skin is cold, the pulse feeble, the head heavy, the countenance stupid, and sometimes the cholera tint remains. Other affections are

a sort of non-febrile delirium, lasting for two or three days, and the spasmodic contractions of the forearm which occur during convalescence. True intermittent febrile attacks, with initial chills, occurring every day during reaction, have also been observed. All these affections are, for the most part, more rapid than when occurring in the individual previously healthy.

PATHOLOGY.—Until more is known of the exact nature of the toxic substances which can be elaborated by the cholera spirillum, when present in the human intestine, no very exact statements of the pathology of the disease can be given. It is evident that an irritation of the intestinal mucosa, with more or less damage to the histological structures, is caused by the spirillum or its products, and that in pronounced cases a very abundant transudate of fluid follows. Many of the symptoms of the disease, especially in the algid stage, are due to the consequent loss of fluid on the part of the blood and tissues of the body. In addition to this loss of fluid there are reflex nervous influences upon the heart and perhaps other parts of the body, due to the lesions in the intestine, and toxic substances absorbed from the intestinal contents probably act upon the cells of the viscera. To these factors, *i.e.*, loss of fluid, nervous reflexes and toxæmia, which account for the symptoms of the disease, may be added an increased susceptibility to secondary infections.

PATHOLOGICAL ANATOMY.—The alterations of the internal organs in a case of death from cholera bear little relation to the violence of the disease. The appearances are about as follows: Emaciation is general, and there is marked lividity of the lips and nostrils. Rigor mortis is not rare before the warmth of the body has wholly departed and is very marked and prolonged. The peritoneal surface is sticky and covered with a viscid exudation (present in 91.6 per cent. of 530 cases); the vessels of the mesentery are engorged with blood. The calibre of the intestinal canal is more often increased than diminished, and always contains some fluid choleraic matter. The fluid is blood serum, containing a variable number of red corpuscles, and the thicker material found in it is made up of intestinal epithelial cells and mucus. The intestinal mucous membrane is usually normal in thickness, but is generally denuded of epithelium. The villi are swollen, giving the surface a velvety appearance, and Peyer's patches and the solitary follicles are much enlarged. The glands of the stomach and of the duodenum are enlarged, and the surface is largely denuded of epithelium. There are no special lesions of the other organs. The liver is rarely enlarged, is the seat of moderate cloudy swelling, and is usually congested with dark thick blood. The gall-bladder generally contains bile, which is at first thicker than normal, but subsequently becomes more abundant and pale. The biliary duct is not obstructed. The pancreas presents no marked alteration. The spleen in rapid cases is small, hard, and wrinkled upon its surface, of a deep red color on section, and sometimes dotted with ecchymoses; in slow cases it may be slightly enlarged and less deep red in color. The blood is thicker than normal, coagulates slowly, and the separation into clot and serum is very incomplete. The corpuscles are not altered in shape, but there is a remarkable diminution in the proportion of water and neutral salts, and a decrease in the amount of fibrin and albumin. The heart is usually soft and flabby, the muscle degenerated, with ecchymoses in the pericardium. The left side is apt to be empty and contracted, the right distended with dark, thick blood. The arteries are, in general, nearly empty, the veins distended with blood. The pleurae are very frequently coated with a glutinous, stringy substance, and ecchymoses often appear in the subpleural cellular tissue. The lungs are usually healthy, but presenting engorgements at the posterior portions; or they may contain pneumonic areas or abscesses due to inhaled vomitus. The bronchi are much congested, and may contain a white, stringy mucus, analogous to that found lining the intestinal canal. The condition of the brain and spinal cord, together with their appendages, is merely that of congestion without special lesion, although it has been

declared that there is a sensible increase in their consistence. The ganglionic system presents no change worthy of notice. The muscles are often engorged with blood, and a very marked reddish-brown discoloration of the bones and of the teeth has been noticed in those dying of asphyxia. Renal congestion is the marked alteration in connection with the genito-urinary tract, and the straight tubules are often completely stripped of their epithelium. The epithelium of the convoluted tubules suffers marked parenchymatous degeneration, even in cases of short duration. In those dying in the cold stage the bladder is empty and firmly contracted. The uterus usually shows a hemorrhagic endometritis, and abortion is the rule in pregnant women.

DESCRIPTION OF THE SPIRILLUM OF CHOLERA.—Asiatic cholera is without doubt due to a special organism—the so-called "comma bacillus" of Koch—this name being a misnomer, for the bacterium is not a bacillus, but a spirillum.

The parasitic nature of the disease was suspected for a long time. A number of observers had noted the presence, in the cells, of bacteria answering the description of this special one, but it was not until the advance in methods of observation had progressed a long way that it was possible to isolate the organism, and study it under artificial conditions in such a manner as to obtain the evidence necessary to connect it with the process as a causal factor. It was in the year 1883 that Koch first discovered and described the spirillum of Asiatic cholera, which he first found during his investigation in Egypt during the epidemic there, and studied further during the following winter in India.

The organism occurs especially in the small intestine, is generally wholly confined to the contents of the intestine and the glandular culs-de-sac, but is occasionally found in the intestinal walls. It is exceptional to find it in any other part of the body, and it is not strange that investigations undertaken with the idea that cholera was a generalized disease were not productive of results. The bacterium is found in large quantities in the dejecta, and sometimes—in fact not infrequently—in almost a pure culture.

In the intestines and in the dejecta it presents the appearance of a short, thick rod, slightly curved in the long diameter, hardly half as long, but considerably thicker than the bacillus of tuberculosis. It usually occurs in this situation singly, but not infrequently it is arranged in pairs, with the curves opposed to each other, and thus recalling the shape of the letter "S." There are many exceptions to this rule, and a simple microscopical examination of the dejecta does not suffice to establish a diagnosis of Asiatic cholera, or to exclude such a diagnosis. Sometimes no curved, S-shaped, or spirilliform organisms are seen, but the preparation contains numerous granules of various shapes. If, however, plate cultures are made from these discharges, they may yield practically pure cultures of the cholera spirillum. Even when very small quantities of the dejecta are used, the colonies may crowd the plates. Under cultivation in bouillon the organism appears longer and thinner, and there are many true spirilla to be seen in the preparations made from such a culture. (See Plate LIX.)

A characteristic that is of especial interest is its extreme motility, which has been demonstrated by Löffler to be due to a fine cilium or two, occasionally three cilia, which are longer than the bacteria, placed at one end of the organism. Shortly before division, both ends possess cilia. After prolonged artificial cultivation the motility is reduced in activity.

Shape and motility are not, however, sufficient to differentiate this bacterium from others with similar characteristics—and there are many that possess such—but the method of development upon the various culture media is entirely characteristic, and, as shown by Koch, is all that is necessary for separating this one in particular from the others that resemble it. It liquefies gelatin, but it does this slowly, and at the same time a certain part of this liquefied portion evaporates, and as a result

EXPLANATION OF
PLATE LIX.

EXPLANATION OF PLATE LIX.

- FIG. 1.—Mucus from the Intestine of a Cholera Patient. Cover-glass preparation, stained with gentian violet. Magnified 800 diameters. (Fraenkel.)
- FIG. 2.—Colony of Cholera Bacilli in Gelatin, after the Lapse of Seventy-two Hours. Magnified 75 diameters. (Plagge.)
- FIG. 3.—Colony of Cholera Bacilli in Gelatin, after the Lapse of Seventy-two Hours. Magnified 170 diameters. (Koch.)
- FIG. 4.—Cholera Bacilli from a Bouillon Culture at the Expiration of Twenty-four Hours. Cover-glass preparation stained with fuchsin. Magnified 1,000 diameters. (Koch.)
- FIG. 5.—Needle Cultures of Cholera Bacilli in Nutrient Gelatin, at the expiration of one day, three days, four days, five days, seven days, and ten days, respectively. (From Koch and Gaffky: "Bericht über die Thätigkeit der zur Erforschung der Cholera im Jahre 1883 nach Egypten und Indien entsandten Commission," Berlin, 1887.)



FIG. 1.



FIG.2.

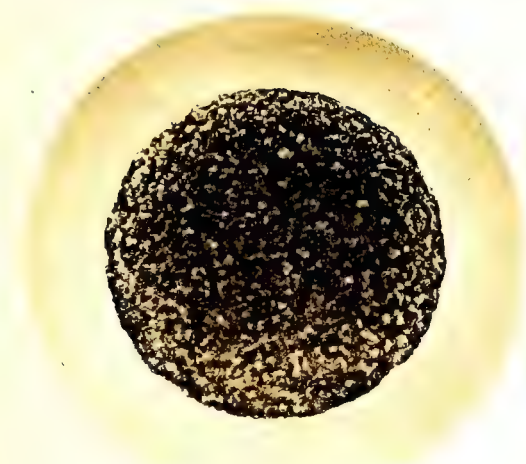


FIG.3.



FIG. 4.

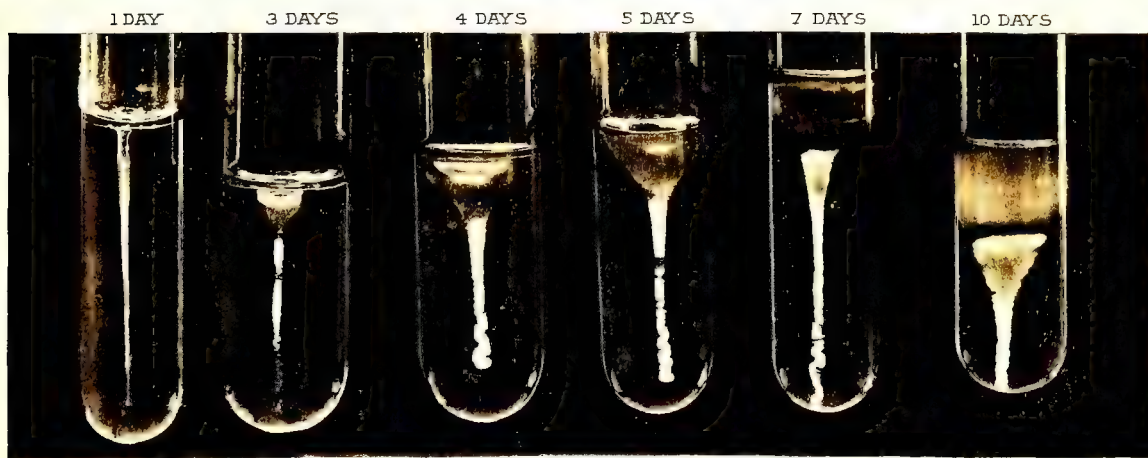


FIG.5.

CULTURES AND STAINED COVER-GLASS PREPARATIONS.
(AFTER KOCH AND GAFFKY.)

there is a special appearance of the culture that is shared by only a few other spirilla. At the upper portion of the gelatin there is a round cavity full of air, and as the surrounding gelatin has remained solid, the appearance is that of a bubble of air in the midst of the upper part of the gelatin and above the liquefied part. The appearance is wholly different when the organism found by Finkler is put under the same conditions, and equally so with the cheese spirillum of Deneke. The spirillum of Metschnikoff grows in very similar fashion in stab cultures in gelatin, and there have been isolated from water and other sources spirilla which cannot be distinguished from the cholera vibrio in this culture medium.

Morphology.—Slightly curved rods, with rounded ends, from 0.8μ to 3μ long, and about 0.3μ to 0.5μ broad. They are usually but slightly curved, like a comma, but are occasionally in the form of a half-circle, or two united rods curved in opposite directions, forming an S-shaped figure. Under certain circumstances these curved rods may develop into long spiral filaments, and in hanging-drop cultures the S-shaped figures may also be seen to form the commencement of a spiral. In stained preparations the spiral character of the long filaments is often obliterated, or nearly so. When development is very rapid, the short curved rods, or S-shaped spirals, only are seen, but in hanging-drop cultures, or in media in which the development is retarded by an unfavorable temperature, the presence of a little alcohol, and so on, the long spiral filaments are quite numerous, and it is quite generally agreed that the so-called comma bacillus is really only a fragment of a true spirillum.

By Löffler's method of staining, the rods may be seen to have from one to three terminal flagella. In old cultures the bacilli frequently lose their characteristic form, and become variously swollen and distorted. Hueppe has described the appearance in the course of the spiral filaments, of spherical bodies which he believes to be reproductive elements, the so-called arthrospores. These bodies are not functionally spores; for cultures containing them are no more resistant than those which contain spirilla without these bodies. The cholera bacillus stains with the usual aniline colors, but not so quickly as many other bacteria. It is best stained by a watery solution of fuchsin. It will not stain by Gram's method. Sections may be stained by Löffler's methylene blue.

Biological Characters.—It is an aerobic, facultative anaerobic, liquefying, motile spirillum, grows in the usual culture media at the room temperature, more rapidly in the incubator, does not develop above 42°C . or below 14°C ., does not form endogenous spores. In gelatin plate cultures, at 22°C ., at the end of twenty-four hours small white colonies may be perceived in the depth of the gelatin. These grow toward the surface, and cause liquefaction of the gelatin in the form of a funnel that gradually increases in depth, and at the bottom of which is seen the colony, in the form of a small white mass. As a result of this, the plates on the second or third day appear to be perforated with numerous small holes; later, the gelatin is entirely liquefied. Under a low power, the young colonies, before liquefaction has commenced, present a somewhat characteristic appearance. They are of a white, or pale yellow color, with a more or less irregular outline, the margins being rough and uneven; the texture is coarsely granular, and the surface looks as if it was covered with little fragments of broken glass, while the colony has a shining appearance. When liquefaction commences, an ill-defined halo is first seen to surround the granular colony, which by transmitted light has a peculiar roseate hue.

In gelatin needle cultures development occurs all along the line of inoculation, but liquefaction of the gelatin occurs at first only near the surface. On the second day, at 20°C ., a short funnel is formed that has a comparatively narrow mouth, the upper portion containing air; just below this is the whitish viscid mass of the growth. At the end of from four to six days, the funnel, having increased in depth and diameter, may reach the walls of the test tube. In from eight to fourteen days the upper

two-thirds of the gelatin is completely liquefied. Owing to the slight liquefaction occurring along the line of growth the first three or four days, the central mass that has formed along the line of inoculation settles down as a curved or irregularly bent yellowish-white thread, in the lower part of a slender tube filled with liquefied gelatin, the upper part of which widens out, and is continuous with the funnel above. (See Fig. 5 of Plate LIX.)

On the surface of nutrient agar a moist, shining, white layer is formed along the line of inoculation. Blood serum is slowly liquefied. On potato in the incubator, a rather thin semitransparent brown, or grayish-brown layer is developed.

In nutrient bouillon the development is abundant and rapid, especially in the incubator. The fluid is only slightly clouded, but the spirilla accumulate at the surface, forming a wrinkled membranous layer.

Sterilized milk is also a favorable culture medium. The milk, however, is not visibly altered by the growth of the bacilli.

In general this organism grows in any fluid containing a small quantity of organic material and having a slightly alkaline reaction. An acid reaction of the culture medium prevents its development as a rule, but it has the power of gradually accommodating itself to the presence of vegetable acids, and grows upon potatoes (in the incubator only) which have a slightly acid reaction. Abundant development occurs in bouillon which has been diluted with eight or ten parts of water, and the experiments of Wolffhügel and Riedel show that it also multiplies to some extent in sterilized river or well water, and that it preserves its vitality in such water for several months, but in milk or water containing other bacteria it dies out in a few days. This organism is destroyed, in recent cultures, in nutrient gelatin at 52°C ., as determined by Sternberg, the time of exposure being four minutes. A few colonies only develop after exposure to a temperature of 50°C . for ten minutes. In Kitasato's experiments ten or even fifteen minutes' exposure to a temperature of 55°C . was not always successful in destroying the vitality of the spirilla, although in certain cultures exposure to 50°C . for fifteen minutes was successful. The low resisting power to heat, desiccation, and chemical agents, indicates that this organism does not form spores, and most bacteriologists agree that this is the case.

Hueppe has described a mode of spore formation which is different from that occurring among the bacilli, that is, the formation of so-called arthrospores. These are said to be developed in the course of the spiral threads, not as endogenous, refractive spores, but as spherical bodies with a somewhat greater diameter and somewhat more refractive; but this method of spore formation has not been observed by others who have investigated the question, and cannot be considered established.

The test for the presence of the cholera spirilla originated by Bujwid and by Dunham consists in the reddish-violet color produced in the bouillon cultures containing peptone, or in cultures in nutrient gelatin when a small quantity (five to ten per cent.) of sulphuric acid is added to the cultures. According to Fraenkel this test serves to distinguish it from the ordinary bacteria of the intestine, and from the Finkler-Prior spirillum, but not from Metschnikoff's spirillum. The reaction is shown by bouillon cultures which have been in the incubator for ten or twelve hours, and by gelatin cultures in which liquefaction has occurred. The sulphuric acid should be quite pure. The color quickly appears, and is reddish-violet or purplish-red. According to Salkowski, the red color is due to the well-known indol reaction, which in cultures of the cholera spirillum is exceptionally intense and rapid in its development.

The most satisfactory method for obtaining the "cholera-red" reaction—as we have had lately abundant opportunity to verify—is that of Beyerinck ("Cat. f. Bact. u. Parasit.," Bd. xii., S. 715) in which cultures are made in filtered neutralized one-half-per-cent. solution of commercial peptone, at 37°C . After twelve to twenty-

four hours the cultures are cooled, and from two to five drops of chemically pure sulphuric acid are added. If the spirillum be present, a very marked and beautiful rose-violet color is produced in the course of a few moments. In peptone-water cultures this indol reaction is perceptible as soon as the faintest clouding of the medium can be observed. Four to six hours' incubation at 37° C. may suffice.

A test which is said to distinguish cultures of the cholera spirillum from the spirillum of Deneke and that of Finkler-Prior has been suggested by Cahen. This consists in adding a solution of litmus to the bouillon, and in making the cultures at 37° C. The cholera cultures show on the following day a decoloration which does not occur at this temperature with the other spirilla named. For determining as promptly as possible whether certain suspected excreta contain the cholera spirilla, a little of the material may be used to inoculate greatly diluted bouillon, or a one-per-cent. peptone, one-half-per-cent. salt solution, gelatin plates being made at the same time. At the end of ten or twelve hours the cholera spirilla, if present, will already have formed a characteristic wrinkled film upon the surface of the bouillon. A little of this should be used to start a new culture in bouillon, and a series of gelatin plates made from it, after which the indol test may be applied. In the peptone solution mentioned above, the cholera spirilla seek the surface of the medium, and if cultivated at 37° C. a little of the material may be taken with a loop from the surface at the expiration of three hours and used for plate cultures or for examination in the hanging drop. The result of this, in connection with the morphology of the micro-organisms forming the film, and the character of growth in the gelatin plates, will establish the diagnosis, if the cholera spirillum is present in considerable numbers; if but few are present in the original material it may be necessary to make two or more series of plates and bouillon cultures before a pure culture can be obtained, and a positive diagnosis made. These tests will suffice for the purpose in times of epidemic cholera, but when there is doubt concerning the existence of cholera in the region, more rigorous identification is desirable. The virulence of the cultures may be tested on guinea-pigs and the agglutinative test with the serum of immunized animals applied.

Pfeiffer has shown that recent aerobic cultures of the cholera spirillum contain a specific toxic substance fatal to guinea-pigs in extremely small doses. This substance stands in close relation with the bacterial cells, and is perhaps an integral part of the same.

The spirilla may be killed by chloroform, by thymol, or by desiccation without apparent injury to the toxic character of this material. It is destroyed, however, by absolute alcohol, by concentrated solutions of neutral salts, and by the boiling temperature, and secondary products are formed which have a similar physiological action, but are from ten to twenty times less potent.

Similar toxic substances were obtained by Pfeiffer from cultures of the Finkler-Prior spirilla, and from the spirilla of Metschnikoff.

The spirillum is not found in the blood, nor in the various organs of individuals dead of cholera, but is always found in the discharges during life, and in the contents of the intestines examined immediately after death, frequently in almost a pure culture in the colorless rice-water discharges. They may persist in the discharges for twenty-three or more days, but usually disappear from the ninth to the twelfth day of the disease. Occasionally they may fail to appear in cultures for one or more days during the attack. It is evident that the morbid phenomena must be ascribed to the absorption of toxic substances formed during the growth of the spirillum in the intestine. In cases which terminated fatally after a very brief sickness Koch found but very slight changes in the mucous membrane of the intestine, which was slightly swollen and reddened; but in more protracted cases the follicles and Peyer's patches were reddened about their margins, and an invasion of the mucous

membrane by the organisms was observed in properly stained sections. They penetrated especially the follicles of Lieberkühn, and in some cases were seen between the epithelium and the basement membrane. As a rule, the spirillum is not present in vomited material, but there are numerous exceptions to this rule on record. All observers have found the organism always present in cases of true cholera; on the other hand, very numerous control experiments fail to show its presence in the intestinal contents of healthy persons, when cholera is not prevalent, or in that of those dead from other diseases.

Nicati and Rietsch observed a certain degree of attenuation in the pathogenic power of the spirillum, after it had been cultivated for a considerable time at from 20° to 25° C., and the observation has since been made that cultures which have been kept up from Koch's original material have no longer the original pathogenic power. They also gradually change in biological characters upon prolonged cultivation, the colonies on gelatin plates being much less glistening and granular.

The organism most likely to be confounded with the cholera spirillum, and from which it must be differentiated by the methods of cultivation, as well as by the aid of the microscope, is the spirillum of Finkler-Prior, otherwise called the vibrio proteus. It was obtained by Finkler and Prior in 1884, from the fæces of patients with cholera nostras, after allowing the dejecta to stand for some days. Subsequent researches have not sustained the view that this spirillum is the specific cause of cholera nostras. Besides this spirillum many others, more or less resembling the spirillum of cholera, have been isolated. With the exception of the vibrio of Ivanoff (Migula), an organism incidentally isolated from the stools of a patient suffering from typhoid fever, none of these spirilla agglutinate with cholera immune serum. The colonies of this vibrio, however, do not closely resemble those of cholera on gelatin plates, being less granular and more filamentous.

Despite the numerous controversies on the subject since the first announcement by Koch that he considered his spirillum to be the cause of cholera, and the many assertions to the contrary, the relationship between the two is to-day admitted by practically all authorities. The opinion to this effect is based upon a number of reasons, some of which are as follows:

1. The spirillum of Koch has never been found in any other disease, a point that has been established by innumerable observations.
2. This spirillum is found in all cases of Asiatic cholera, without exception, provided that the case is not too far advanced. In such a case there has been a secondary infection, that has killed out the true organism and masked its effects. Ever since the first announcement of this discovery by Koch, observers have verified his assertions in all parts of the world where cholera has been investigated.
3. This spirillum is found in slight cases as well as in severe. It is present in the beginning of the attack, and it is located in the intestine, that is to say in the region especially attacked by the disease, and in which occur the initial and essential lesions.

The attempts to add to these arguments the more decisive one of successful inoculation experiments, were at the first not satisfactory in their results. Nicati and Rietsch were the first to secure successful results, which they obtained by introducing pure cultures of the organism into the duodenum of guinea-pigs, in which animals they had previously tied the ductus choledochus. By these experiments they obtained symptoms extremely analogous to those of true cholera, and Koch also succeeded in the same direction by passing the infectious material (pure cultures) into the stomach by an œsophageal catheter. In his experiments the animals had been previously narcotized by the injection of tincture of opium, to prevent peristalsis, and their stomachs had been made alkaline by the introduction of carbonate of soda, a solution to make the contents of the stomach

alkaline being necessary, because the spirillum of Asiatic cholera will not develop in an acid medium.

Doyen has shown that by introducing alcohol into the stomach the alkaline solution and the tincture of opium may be dispensed with. But, however the experiments may be conducted, they all show one important thing—the great necessity for a healthy condition of the gastro-intestinal tract for the avoidance of infection with cholera. Dyspeptics and alcoholics have been shown in all epidemics to be especially fatally attacked by the disease. It cannot yet be affirmed that the absolute proof of the production of cholera by the specific spirillum has been obtained, because the methods employed in the experiments mentioned above leave too many loop holes open for the occurrence of accidents, and yet the evidence is so nearly complete that there seems to be no reason for any doubt; the more especially as the exact experimental evidence can probably never be obtained, because none of the lower animals, so far as is known, are susceptible to cholera under natural conditions. The nearest approach to an actual experiment upon man is the case of one of the members of one of the cholera courses held in Berlin in the winter of 1884–85. This man, a physician, was attacked with “cholera,” and after some suffering, but no dangerous symptoms, recovered, the cholera spirillum being isolated from the discharges at various times during his illness. There seems to be no doubt that this was a case of true cholera, arising from some carelessness upon the victim's part in handling the cultures with which he had to deal in the laboratory, for there were no cases of cholera in Berlin at the time, nor had there been for a long time previous.

The famous experiments of Pettenkofer and his pupils and similar experiments by Metschnikoff, in which cultures of cholera spirilla were deliberately swallowed, do not militate against the etiological importance of that spirillum. These experimenters suffered from symptoms similar to those observed in the milder forms of epidemic cholera, and the dejecta were similar in character and contained the spirilla in like numbers.

The entrance of the spirilla is undoubtedly effected by means of the gastro-intestinal tract, and there has not been a particle of evidence from experimental work to favor the theory of Pettenkofer that it may enter from the air and through the respiratory organs.

The acidity of the gastric juice is extremely unfavorable to the growth of the organism, and this explains the liability of the persons with functional or organic disease of the stomach to attacks of the disease, for in these instances the reaction of the gastric juice is altered or modified so as to allow the spirillum to pass this point of danger and reach the intestine, where there are more favorable conditions for its development. Diluted hydrochloric acid (0.05 per cent.) is said to kill the spirillum in six minutes. In the presence of pepsin 0.019 per cent. of acid suffices. Water, taken on an empty stomach, excites very little acid secretion—in fifteen minutes from 0.011 to 0.03 per cent. These quantities are entirely too small to prevent the passage of the organism.

Nicati and Rietsch, and Van Ermengen determined the toxicity of cultures of this organism when they had been deprived of the bacteria by filtration or when the bacteria had been killed by heating. In 1885 Nicati and Rietsch, by treating similar cultures with alcohol, succeeded in extracting a substance that killed guinea-pigs and rabbits, with the production of cramps and a lowering of temperature. Brieger studied the various chemical bodies that appeared in the cultures of the cholera spirillum; among the number there were convulsants, methyl guanidin and a base, $C_3H_8N_2$, a febricant poison, and compounds that produced inflammation and necrosis. More recently, Brieger and Fraenkel have isolated a toxalbumin, and Petri has determined the presence of a less active substance, toxopeptine.

Hueppe and Scholl have perhaps made as important researches as any in their work upon cultures that have been deprived of free access of oxygen. From such cultures they succeeded in obtaining a peptoxin that in a

dose of 5 c.c., killed guinea-pigs in forty minutes, the animal presenting paralytic symptoms after ten minutes and convulsions after a quarter of an hour. This is a more active poison than was obtained before and was got in larger quantities; an egg after inoculation with a pure culture produced at the end of eighteen days enough to cause the death of ten guinea-pigs. The importance of this is seen when it is remembered that the spirilla are deprived of the access of oxygen when they are developing in the human intestine, and according to these experiments are therefore under the most favorable conditions for the development of this particular toxin.

Numerous experiments have shown that fluid artificial media do not usually become very toxic when cholera spirilla are grown in them. If they be filtered before the vibrios have died off to any considerable extent the filtrate is not highly toxic, while the residue, consisting largely of the bacteria themselves, is toxic in very much greater degree, even if heated sufficiently to kill the bacteria. That diffusible toxins may be produced in the animal body was shown by Metschnikoff, Roux, and Taurelli, who sealed cultures of cholera in collodium capsules which were introduced into the peritoneal cavities of animals with fatal results. The chemical nature of these various toxic substances is unknown.

A temperature of from 30° to 40° C. is the most favorable for the development of the cholera spirillum, but it will grow slowly at a temperature as low as 17° C. It ceases to grow at a temperature lower than this, but its vitality is not destroyed, and it grows well when the temperature is again raised; at –10° C. its vitality has been retained, but, on the other hand, heating to a temperature as low as 56° or 60° C. is sufficient to destroy its vitality in a short time.

Inasmuch as no true spore formation has been seen to occur in the development of this organism, it is not surprising that drying was shown, first by Koch, to destroy its vitality in a very short time—less than twenty-four hours. But conclusions drawn from his experiments may be misleading, for while this destruction of vitality by drying does occur in a very short time in the case of thin layers, it does not take place under less favorable conditions. This was shown by Kitasato, and by Berkholz, who saw the vitality retained, the one for thirteen days and the other for thirty-eight, in experiments in which silk threads were used for holding the organism during their subjection to desiccation. It should be said, however, that these experiments were conducted in a desiccator, which did not permit the free access of oxygen to the bacteria, and it is undoubtedly the case that this agent is as important as any in the production of the result that it was desired to obtain. On the other hand, desiccation was probably more complete than would usually be the case under more natural conditions.

The organism has been found in ordinary drinking-water by Koch in one of the tanks in India, in the neighborhood of which an epidemic of cholera had broken out. It does not live long in distilled water, however, as shown by Meade Bolton, Wolfhügel and Riedel, and others. Strauss and Dubarry found that it lived for fourteen days in one case, and Kraus, for two days only. Other observers have not seen it retain its vitality for anything like so long a time. In ordinary sterilized water it lives longer, according to the experiments of Wolfhügel and Riedel, as well as Pfeiffer, who found that it existed for seven, nine, and twelve months, while Hochstetter lengthened this time to three hundred and ninety-two days. And more recently viability has been observed after nearly two and a half years. Its vitality appears to be shorter again in non-sterilized water. Strauss and Dubarry found it to be thirty days in one specimen, and thirty-nine in another; while a mixture of other bacteria shortens the time still more. This latter point is one of great importance and has been studied by many experimenters. Koch determined that the organisms ceased to live in ordinary drinking-water at the end of six or seven days, and that after twenty-four hours' contact with sewer water they appeared to be dead;

while Schiller, on the other hand, found that they retained their vitality in the same medium for fourteen days. Petri, in an effort to find out how long they lived in the intestine after burial, was able to demonstrate them in cultures at the end of nineteen days. Certain foods may be of great importance in transmitting the organism, as in the case of milk, in which it grows with great energy and without producing the least visible alteration; it has been shown that it will live for at least four days in milk and forty-eight in butter.

Most of these experiments were conducted with the idea that this organism is an aerobic one, but Hueppe has shown that it is also anaerobic, and that grown under these conditions the spirillum is possessed of a greater virulence, but it is also easier of destruction. As suggested by Proust, this may explain the comparative rarity of immediate infection. The bacterium coming from the intestine as an anaerobic organism is possessed of feeble resisting powers and is therefore easily destroyed, and it is only after it has taken on the conditions of aerobic growth that are furnished it in the medium in which it develops outside of the body that it finds itself possessed of the power of resistance sufficient to enable it again to enter the human body. Such observations are of especial interest in connection with the theory of Pettenkofer (*vide supra*), as seeming to show that his idea of the influence of locality is exact, in so far as this influence is exerted in changing the anaerobic to aerobic conditions of growth and effecting an adaptation of the organism to this change.

According to Koch, solutions of 1 in 400 of carbolic acid, 1 in 2,500 of sulphate of copper, and 1 in 10,000 of corrosive sublimate are sufficient for the arrest of the development of the spirillum of Asiatic cholera. Esmarch and Eisenberg show that creolin will destroy it more quickly than carbolic acid in solutions of the strength of from 1 in 1,000, or 1 in 2,000. Liborius, Kitasato, and Pfuhl have shown the active effect of freshly prepared milk of lime, while Hueppe and Loewenthal convinced themselves of the important prophylactic and therapeutic value of salol in the management of cholera.

TREATMENT.—*Inoculation Against Cholera.*—The first efforts to confer active or passive immunity to cholera in the human subject were made by Ferran, a Spanish physician (Report to the Academy in Barcelona, July 16th, 1884), who attempted to immunize more than twenty-five thousand people during 1885, when cholera was epidemic in Spain. His method consisted in the subcutaneous injection of increasing amounts of virulent cultures of the cholera vibrio, five or six days being allowed to elapse between successive injections. Three such injections were regarded by him as fully protective against the disease. He also employed injections of blood from those who had recovered from cholera to protect others from attacks of the malady. His enthusiastic claims for the efficiency of these prophylactic measures were discredited by other observers, and there appears to be no doubt that his methods were faulty. The purity of his cultures is open to question and his claims were exaggerated. But his conceptions were the same as those which subsequently led to more careful and promising work in this direction, and the credit of priority belongs to him.

Since these early attempts of Ferran, which were based upon studies of the immunization of guinea-pigs at a time when proper methods had not been elaborated, numerous investigators have experimented on animals in this direction and have obtained results which throw considerable light on the character of the immunity that can be conferred upon animals, and presumably upon man.

One of the difficulties encountered in this work is due to the fact that the lower animals do not respond to cholera infections so as to present a well-defined disease comparable to human cholera. Fatal results may follow intravenous, subcutaneous, or intraperitoneal inoculations with cholera cultures, and also after the introduction of cultures into the stomach. But special preparation of the animals for this last mode of inoculation is usually nec-

essary. The procedure for this purpose, devised by Koch for guinea-pigs, was the neutralization of the stomach contents with sodium carbonate, and the checking of intestinal peristalsis with a subcutaneous injection of tincture of opium. If, after this preparation, the animals receive cultures of the cholera vibrio, introduced through a stomach tube, they develop symptoms which bear some resemblance to the algid stage of cholera. The temperature falls, the skin becomes cyanotic, and great muscular weakness is manifested by inability to walk or stand. Occasional muscular spasms are frequently observed and the animals die after several hours. These symptoms do not develop immediately after the inoculation, and there is evidently a very considerable multiplication of the vibrios in the intestine. At autopsy the serous coat of the intestine is injected, the intestinal wall is swollen, and a serous fluid containing desquamated epithelium fills the bowel. There are usually no evacuations, though occasionally a thin serous fluid escapes from the anus.

While these manifestations bear some resemblance to the algid stage of human cholera, the results of such inoculations cannot be regarded as satisfactory reproductions of this disease. In 1893 Metschnikoff published observations showing that young, suckling rabbits might be inoculated with minute quantities of cholera vibrios placed in the mouth, and that they then developed a fatal disease more closely resembling human cholera than that obtained in guinea-pigs by Koch. This was subsequently shown to be the case when very young kittens or puppies were employed. We shall have occasion to refer to these experiments again.

Experiments with a view of determining the possibilities of immunizing against cholera have been very numerous. Most of the observations have been made on guinea-pigs, though other animals have also been employed. It has not been difficult to attain positive results in many different ways. Intraperitoneal, subcutaneous, or even intravenous inoculations with non-lethal amounts of living cultures of cholera vibrios is followed within a few days by a species of immunity manifested by bactericidal or bacteriolytic properties of the serum of the animal. Such animals will then survive inoculations with virulent cultures in amounts which considerably exceed those regularly fatal to normal animals. Similar results may be obtained by the use of dead cultures, whether the vibrios have been killed by heat or by the addition of germicides. Such animals also are immune against inoculation with virulent cultures in considerable amount. This immunity, whether caused by living or by dead cultures, protects the animals against inoculations into the blood, peritoneum, or beneath the skin; but appears to have little if any effect upon the course of the disease when cultures are introduced into the mouth or stomach. This fact was strikingly manifest in experiments in very young animals, which, as stated above, readily acquire a form of cholera when very small amounts of cultures are introduced into the mouth. Moreover, very large amounts of cholera cultures introduced into the blood or peritoneal cavity cause death in immunized animals in spite of their protection against moderate lethal doses. Large doses of dead cultures also cause death. A fact worthy of note is that filtered recent cultures of the cholera vibrio are neither very toxic nor useful for immunization.

The results of the experiments mentioned above lead to the inference that the introduction into the body of non-lethal quantities of the vibrio calls forth the production of anti-bodies that are destructive to the vibrio if they are brought into contact with it, but that they are not capable of neutralizing toxic substances that appear to be closely associated with the bodies of these micro-organisms if not actually a part of their structure. The immunity obtained is due to bacteriolysis and not to antitoxins. We may, therefore, fatally poison an immune animal with cholera cultures though it be capable of destroying a limited number of cholera vibrios which are brought into its tissue fluids.

It has been shown that the blood and serum from patients who have recovered from attacks of cholera also contain these or similar bacteriolytic substances, but there appears to be no antitoxic substance in these fluids.

These bacteriolytic anti-bodies do not exist to an appreciable extent in the blood of convalescents immediately upon recovery, but are distinctly active about three weeks after the attack, then gradually accumulate or increase in potency until a maximal efficiency is reached between the fourth and sixth weeks. At this time 0.01 c.c. of the blood may be enough to protect a guinea-pig from the effects of an otherwise fatal intraperitoneal infection with cholera. After the sixth week the bacteriolytic value of the blood gradually declines and is lost after about three months.

To emphasize still further the character of this immunity, experiments may be cited which show that animals which have been inoculated with cholera vibrios in amounts ordinarily sufficient to kill, may be saved if they receive injections of serum from immunized animals within from one-half to two hours after the inoculation, before symptoms referable to intoxication have developed. When these symptoms have declared themselves the treatment is without avail, *i.e.*, if the disease can be checked by destroying the vibrios already in the system, the immune serum will protect; but if there is already in the body a dose of toxic substances sufficient to kill, the immune serum is powerless to neutralize them. These toxic substances appear to be present in lethal quantities in the majority of cases, as soon as symptoms of disease become manifest.

A question of great practical importance is whether these protective, bacteriolytic anti-bodies which are present in the blood and lymph can pass into the digestive tract and act upon cholera vibrios present in the intestinal contents. Experiments upon animals, already cited, appear to answer this question in the negative, but it is doubtful whether these results can be directly applied to man. If Ferran's claims are justified by the facts, such direct application of animal experiments cannot be made; for an active immunity caused by subcutaneous injections of cholera vibrios would appear to protect against infection by way of the mouth in human subjects, though they failed to do so in animals. It was the belief that such was the case that induced Haffkine to undertake the immunization against cholera by a method essentially similar in principle to that employed by Ferran, but safeguarded by a more highly developed technique.

Haffkine experimented with his method of immunization in India, aided by the Government, and between 1893 and 1895 had subjected about forty thousand people to his prophylactic treatment. This consisted in the subcutaneous injection of living cultures of the cholera spirillum of definite and known virulence. The first injection was made with a culture of moderate virulence, attenuated by long artificial cultivation and taken by him to India from the European laboratories.

These injections were made only after a microscopical examination of a stained smear had failed to reveal contamination of the culture and revealed well-formed, apparently normal cholera vibrios. The injections were made under strictly aseptic conditions. During the first two hours after the injection there were no appreciable effects either locally or constitutionally. Between the third and twelfth hours there was a gradually developing tenderness at the point of inoculation with general malaise and fever. In normal cases the fever reached 101° F., but would sometimes reach 104° when the susceptibility of the patient was great. The amount of culture injected depended upon the age of the patient; for an adult man the amount being about 1 c.c. From the twelfth to the thirty-sixth hour after the inoculation the general symptoms gradually but completely vanished and a painful induration at the point of inoculation developed. This also subsided in the course of a few days. No digestive disturbance was occasioned by the inoculation, and no change of diet or occupation was necessary.

The second inoculation was made about five days after

the first. For this purpose a highly virulent culture, kept active by passage through susceptible animals, was employed, the dosage being determined by the reaction obtained after the first injection. The effects of this inoculation were essentially the same as those obtained after the first, but were usually less pronounced. The immunizing action was believed to be complete six days after the first inoculation. Up to 1896 over one hundred thousand people are said to have received this treatment.

The results of this treatment, which was purely preventive, not curative, are reported as being very promising. Several of those so treated contracted cholera shortly after the first injection, showing that its protective action was not immediate. Haffkine believed that the full protective action was attained in about twenty days. Comparative statistics, when of a given group about half were inoculated, were greatly in favor of the value of the method. The protection was not lasting, however, and seems to have gradually passed away, some twelve months being the probable limit of its efficiency. The protection is not absolute, and the mortality among those who have been inoculated and yet acquired the disease is but slightly less than among the uninoculated. About one-nineteenth as many cases occurred among the inoculated and about one-seventeenth as many deaths. Of late years this method appears to have fallen into disuse. This is not surprising when the difficulty of inoculating a whole population, the evanescent character of the protection, and the uncertainty of its absolute value are considered.

Upon theoretical grounds, as already stated, but little can be expected from a bacteriolytic serum injected beneath the skin in human cholera; for the vibrios are situated in the intestinal contents and the crypts of the intestinal mucosa.* To be effective the protective constituents of the serum must come in contact with the bacteria they are to destroy. It appears doubtful whether these elements enter the intestinal lumen when present in the blood. A serum which had antitoxic properties should be much more efficient. Pfeiffer has shown that the most active toxic substances produced by the cholera vibrio are intimately connected with the bodies of the organisms when the latter are grown in artificial media. In 1896 Metschnikoff, Roux, and Taurelli-Salimbeni made experiments with a view of demonstrating that soluble toxins might be obtained from the cholera vibrio as a species of secretion. They obtained a highly poisonous toxin, not destroyed by boiling, of which one-fourth of a cubic centimetre killed a guinea-pig weighing 300 gm. in eighteen hours. They also showed that it was possible to obtain an antitoxic serum by immunizing animals with this toxin. But this serum failed to cure young animals infected by the mouth with cholera vibrios. As yet, therefore, there is no known serum therapy for cholera.

In the absence of a specific antitoxic or other remedy for cholera, recourse must be had to measures directed against morbid conditions as they arise.

A very great number of remedies have been employed with a view of destroying the cholera spirilla in the intestinal tract, or, at least, of inhibiting their multiplication. Among these remedies are: chlorine water, mercuric salts, salts of copper, iodine, iodoform, creosote, creolin, cresol, resorcin, thymol, pyoktanin, benzoic acid, salicylic acid and its salts, salol, tribromsalol, tribromphenol, bismuth, benzoyl-acetyl peroxide, etc. It cannot be said that the clinical evidence in favor of any of these remedies is strong, and upon theoretical grounds their utility is very doubtful since the great dilution they suffer in the intestinal tract must render them almost inert. The same appears true of the proposed treatment with mineral acids in eight- to ten-drop doses, diluted with water.

We have already seen that during epidemics of cholera mild cases of this disease are of not infrequent occurrence. These cases are indistinguishable in many in-

* The efficacy of the bacteriolytic serum when administered by mouth or in enemata does not appear to have been tested. It would be worthy of trial.

stances from attacks of simple diarrhœa due to intestinal irritation or indigestion, though frequently unaccompanied by pain. The only safe rule at such times is to regard all cases of diarrhœa as choleraic and as the possible beginning of a serious attack. The patient must be put to bed and isolated. The dejecta should be regarded as likely to contain the cholera spirilla, and carefully disinfected before being disposed of. A warm bath, with warm compresses on the abdomen, has been recommended. The diet should be restricted to fluids, previously boiled. Thirst may be relieved with boiled or carbonated (not alkaline) water. There are differences of opinion regarding the measures appropriate to the treatment of the diarrhœa. The usual practice is to employ some preparation of opium to check the discharges. The tincture given in small, frequently repeated doses has given good results. As it is important to allay all intestinal irritation it must be a matter of judgment in each individual case whether it be wiser to endeavor at once to check the diarrhœa or whether a freer evacuation of the bowels to discharge any irritating contents should be attempted. For the latter purpose calomel in repeated moderate doses, given until the stools become greenish, has a good reputation. Castor oil, emulsified with mucilage of acacia, peppermint water, and syrup, has also been employed. It is thought that calomel is partially converted into mercuric chloride in the intestine, and that it thus exerts some antiseptic action; but to what extent this is true is not known. As an antiseptic sodium sulphocarbonate, in fifteen- to twenty-grain doses for children and thirty-grain doses for adults, repeated every three or four hours, has been used with asserted beneficial effects. To check the diarrhœa, besides opium, astringents have been used and recommended, and to relieve pain the compound tincture of camphor has been employed. The prevalent opinion, however, is that opium fulfils the requirements better than other drugs, and that rest, warmth, and an appropriate diet are of the utmost importance. Tea and moderate stimulation with brandy may be used according to the indications.

Should the symptoms persist and vomiting set in notwithstanding the treatment indicated above, the copious enemata of tannic acid, recommended by Cantani, may be resorted to.

Long before the epidemic of 1866 Dr. Murray, in India, had recommended the half-hourly injection of a pint of a weak solution of common salt and carbonate of sodium into the rectum at a temperature of 120° F., and is said to have obtained very striking results. Similar means were employed by Sansom (*The Practitioner*, November, 1892), in 1866. Cantani advises the addition of tannin to the hot water. From eighty to three hundred and twenty grains are dissolved in three pints or a quart of water or chamomile infusion at a temperature of 102° to 105° F., and twenty drops of laudanum and an ounce or an ounce and a half of gum acacia are added. Instead of tannin, thymol in solution of hot water (1 in 1,000) has been recommended by other authorities. In the recommendations of the Royal College of Physicians (1892), benzoate of sodium, two drachms to a quart of water, has been suggested as an alternative to the tannic acid. In every case the injection should be made with much gentleness. The best position of the patient is that on the back with the hips well raised and the legs well drawn up as for lithotomy. The reservoir douche enema should be used and not the ordinary pump. There is much room for doubt as to whether the addition of any medicament to the hot water is of any special value, the favorable results being due probably to the clearing away of irritant and offensive *débris*, to the absorption of fluid from the intestinal surface, and to the relaxation of the arterial spasm by the hot and moist application; but up to the present time the use of tannic acid persists and is recommended. If more than two quarts are injected, a weaker solution should be employed. These enemata may be repeated several times in twenty-four hours. As shown by Cantani, the hot

saline solution may pass through the ileo-cæcal valve into the small intestine.

If signs of improvement do not soon follow the procedure described above, and the algid stage of the disease supervenes, recourse should be had to the second method, of introducing fluid recommended by Cantani and called by him "hypodermoclysis," and consisting in the injection of a hot saline solution into the subcutaneous tissue. About one drachm of common salt is dissolved in a quart of distilled water at a temperature of 100° to 105° F. The apparatus for this should consist of a glass funnel with a long rubber tube attached to a hypodermic needle of fairly large calibre. The needle is introduced in the gluteal, interscapular, lumbar, or ilio-costal region, the funnel being held at about the level of the patient, and the needle pushed so far in that it may be moved freely in the subcutaneous tissue. The reservoir is then elevated slowly so that the fluid runs into the tissue by the force of gravity and its distribution is aided by the manipulation of the fingers. When about half of the fluid has been introduced the needle is removed and the remainder is injected in another place. The method seems to be rational and is supported by strong evidence by Cantani, who has made extensive use of it. It was also extensively employed in the Hamburg epidemic. It is easier of application than the older method of intravenous injection that has been employed for many years, and it seems to be attended with better permanent results. Either or both of these methods must be employed earlier than is usually the case, and before the actual symptoms of death have made their appearance; to wait too long is to throw away all chances of success. The amelioration of the symptoms is usually very striking and prompt, due to the introduction of fluid and warmth; but improvement is frequently of short duration. The procedure may be repeated if the indications for it return; but experience has led to the belief that three or four injections of a quart or more are all that are likely to be beneficial.

Rest and quiet being of the greatest importance, owing to the exhausting nature of the disease, it must be a matter of judgment to what extent active measures to combat the conditions as they arise are wise. The patient should be kept as quiet as is compatible with proper care.

During collapse the condition of the circulation excites most solicitude. When the pulse at the wrist is lost and cyanosis appears, the most efficient remedy is the injection of fluid either intravenously or beneath the skin, as already described. Where the loss of fluid is less pronounced, careful stimulation with cold champagne or brandy and water may be tolerated by the stomach. Subcutaneous injections of ether or nitroglycerin, if used with care and not contraindicated by the condition of the patient, may give good results. Inhalations of small doses of amyl nitrite may also prove beneficial. In the early stages of the disease opium may be used to relieve pain, for it also tends to check the diarrhœa. But in the later stages, when there is danger of collapse, this drug should be avoided. Pain must then be relieved by other means, such as hot applications, moderate counter-irritation, inhalations of chloroform, or subcutaneous injections of camphor rubbed up with olive oil in the proportion of one part of camphor to nine parts of oil sterilized by heat. Gentle massage may give relief from pain, but is likely to disturb the patient more than is wise.

Thirst can best be relieved by ice held in the mouth, cold carbonated water, or nourishing fluids given in small amounts and at frequent intervals.

To prevent loss of heat, the patient should be kept in a warm room, the skin should be kept as dry as possible without disturbing the patient, and he should have dry heat applied by means of hot-water bottles or warm bricks; or the temperature may be maintained by hot compresses.

After recovery from the severe stage of the disease the treatment must follow the indications as they arise. Particular attention must be given to the diet, relapses being frequently traceable to neglect in this direction.

Prophylaxis.—Two principles govern the measures

which should be taken to avoid cholera. The first looks to the exclusion of living cholera spirilla from the gastro-intestinal tract; the second refers to preserving any natural resistance, particularly on the part of the intestine, to injury due to the presence of that organism in the intestinal contents. It is believed that the toxins produced by the cholera spirillum are not absorbed through intact intestinal epithelium, but gain entrance to the circulation only after the epithelium has become damaged, necrosed, or desquamated. Therefore all dietary indiscretions which might cause intestinal irritation are to be avoided. Over-fatigue and exposure to cold are to be carefully guarded against. But it appears wise not suddenly to change the ordinary mode of life, but simply to follow the usual habits in a temperate manner. The free use of alcohol appears to be extremely dangerous. Those addicted to its use are particularly susceptible, and when attacked by the disease the prognosis is bad in people of intemperate habits. Care in the character of the food is important. All articles which might carry infection should be avoided entirely, or partaken of only after being cooked. This is especially the case with water and milk, which should be heated to the boiling point. Prolonged boiling is not necessary, but to insure the death of the spirillum it is safest actually to boil liquid articles of food. It has been recommended to take acid drinks, such as very weak hydrochloric acid, as a prophylactic measure, but it seems doubtful whether this is a wise measure, in view of the danger to the digestion if sufficient acid be taken to act as an effective agent in killing the spirillum. Particular care should be exercised against infection by those attending cases of cholera. They should disinfect the hands immediately after they have come in contact with the dejecta or vomitus from the patient. A two- or three-per-cent. solution of carbolic acid, 1 in 1,000 solution of mercuric chloride, or a solution of "chloride of lime" may be used for this purpose. It is possible that peroxide of hydrogen might find useful application for this purpose and in cleansing the patient, particularly for rinsing the mouth; its freedom from toxic properties and odor and its acid reaction particularly commending it.

The public measures for preventing the spread of cholera must be directed toward the destruction of the spirillum, and, when that is not possible, the checking of its dissemination. Each case that occurs must be regarded as a possible centre from which other cases may arise. The patient must, therefore, be isolated and the utmost care taken to destroy all the spirilla in the dejecta and vomitus, on the bedding and clothing, and on the hands or persons of those attending him. As the patient must be kept as quiet as possible, the evacuations must be received in a bed-pan and disinfected before being disposed of. For this purpose milk of lime has been found very efficacious. This may be prepared as follows: One volume of quicklime, which must not be air-slaked, is placed in a large vessel containing an equal volume of water. This is gradually absorbed by the lime, which then falls to powder. Three volumes of water are then added and the whole is stirred to a thin creamy fluid. Of this equal parts should be added to the dejecta and the mixture allowed to stand for an hour, when disinfection may be considered complete. Fresh "chloride of lime" may also be used, a large heaping tablespoonful of the powder being added to each quart of the evacuations and thoroughly mixed with them. In half an hour the mixture may be regarded as harmless. The hands of the attendants should be disinfected immediately after coming in contact with the patient. The supernatant fluid obtained by mixing 2 parts of fresh "chloride of lime" and 100 parts of water, shaking, and allowing the sediment to settle, may be used, or a two- to three-per-cent. solution of carbolic acid, or 1 in 2,000 corrosive sublimate. These solutions may also be used to cleanse the patient. Sheets and linen may be soaked in 1 in 1,000 solution of corrosive sublimate, the above solution of carbolic acid, or in a three-per-cent. solution of green or soft (potash) soap, with or without the addition of five per cent. of

crude carbolic acid. The fluid must completely cover the articles. The simple soap solution must act for twenty-four hours; the carbolized soap solution will disinfect within twelve hours. Weak formalin, two per cent., may also be used where its odor and irritating properties are unobjectionable. In emergencies, where facilities for carrying on such disinfection cannot be obtained, boiling or burning may be employed to destroy the spirilla.

The bodies of the dead should be disinfected or wrapped in a sheet wet with 1 in 1,000 corrosive sublimate solution, and placed in a tight coffin upon a layer of some absorbent material. The sick-room must be disinfected with sulphurous acid or formaldehyde, or thoroughly washed with 1 in 1,000 corrosive sublimate, and be well aired and dried out before being again occupied.

Harold C. Ernst.

Revised by Edward K. Dunham.

ASPIRIN is the monoacetic acid ester of salicylic acid $C_6H_4 \cdot O \cdot COCH_3$, $\cdot COOH$. It occurs as a white crystalline powder with a melting-point of $135^\circ C$. Is almost insoluble in cold water, but rather freely soluble in alcohol and ether. Heat and alkalies, such as sodium bicarbonate and ammonium carbonate, decompose the product. It is incompatible with antipyrin; it should be kept in a cool, dry place in securely stoppered bottles.

Owing to the insolubility of aspirin in acid fluids, it is thought to pass unchanged through the stomach and be decomposed in the alkaline secretions of the intestine, with liberation of salicylic acid. It therefore should not influence digestion or the functional action of the stomach. Nor does it influence the heart's action or produce unpleasant nervous symptoms. It is antipyretic, analgesic, antirheumatic, and intestinal antiseptic through the action of its salicylic-acid content.

The therapeutic application of aspirin includes its use in cases where the salicylates are indicated. It relieves the pain and reduces the swelling in rheumatic fever; it is useful in muscular rheumatism, in chronic rheumatic affections, gout, and arthritis deformans. It has also been employed in neuralgia, including sciatica, in influenza, pneumonia, the pain of pleurisy, and it is said to be of service in diabetes, chorea, etc.

The dose is from 0.3 to 1.0 gm. (5 to 15 grains) given in tablets or wafers, followed by copious draughts of water. It should never be given in conjunction with alkalies or alkaline waters.

John W. Wainwright.

ATOXYL is the acid sodium salt of arsenic acid, in which one hydroxyl of the arsenic acid has been replaced or substituted by a molecule of aniline. It is a white powder with a faintly salty taste, soluble in warm water to twenty per cent., or to seventeen per cent. in water at $15^\circ C$. Upon standing, aqueous solutions of atoxyl turn a yellowish tint; the same follows the boiling of an aqueous solution. It is said to contain one-fortieth the toxic properties of arsenic acid or one-twentieth that of arsenous acid.

Autopsies showed that animals which had been given poisonous doses of atoxyl possessed the typical lesions of arsenic poisoning, such as hemorrhages from the kidneys, etc. It is indicated in conditions calling for arsenic, and its employment materially shortens the course of treatment from the fact that much larger quantities of arsenic are absorbed without giving rise to the collateral effects where arsenic is pushed. It has been favorably reported upon in skin, nerve, and blood disturbances. Nutrition is improved in tuberculosis, while favorable results have been reported in anemia, chlorosis, neurasthenia, hysteria, sciatica, spasmodic asthma, furunculosis, angina pectoris, contracting kidney, arteriosclerosis, malaria, and syphilis. Robert Koch, who was sent by the German Government to East Africa to study trypanosomiasis (sleeping sickness), reports atoxyl a specific. Much has been written concerning the use of atoxyl in syphilis. Metchnikoff claims that infection can be prevented, two weeks after exposure,

by injecting the remedy around the point of infection. Later stages of the disease are said to yield to atoxyl treatment.

Like other arsenical preparations atoxyl may produce toxic symptoms if pushed too rapidly; indeed, Borneman reports a case of blindness from optic-nerve atrophy following the injection of 27.0 gm. of atoxyl in twenty-per-cent. solution covering a period of three months' treatment for lichen ruber planus. There was arsenical hyperkeratosis of the palms and soles, and arsenic was found in the stools three weeks after the last injection. Such heroic dosing should be refrained from, and the patient should be watched closely during treatment.

The average dose of atoxyl is from 0.02 to 0.05 gm. ($\frac{1}{2}$ to $\frac{3}{4}$ of a grain) hypodermically. It may be gradually increased to 0.2 gm. (3 grains). When such doses are used its application should take place twice a week. Intravenous and intramuscular injections have been employed, but subcutaneously it meets all requirements, as it is not irritating. Solutions should be boiled to sterilize before injections. Atoxyl may be given in conjunction with Blaud's mass and quinine.

John W. Wainwright.

AUTOLYSIS.—*Synonyms*—Autodigestion, self-digestion, autocytolysis. *Definition.*—The digestion of cells, protoplasm, or the proteins of body fluids, by the enzymes which they normally contain.

As the first step in the discovery that living cells may contain enzymes capable of digesting proteids, may be counted the old observation that amoebæ are able to digest solid masses of protoplasm that they have engulfed, by virtue of digestive enzymes contained within their own cytoplasm. The next step was the observation by Hoppe-Seyler, in 1871, that the dead tissues within the body may undergo liquefaction without putrefaction, and that the process resembles the action of the digestive enzymes. It was not until 1890 that the real nature of autolysis was first brought out by Salkowski, who showed that the softening of dead tissues preserved from putrefaction was a true process of digestion brought about by intracellular proteolytic enzymes, and yielding tyrosin and leucin just as in pancreatic digestion. But little more work was done upon this subject until 1900, when it was again opened up by the studies of Jacoby, and since that time it has been investigated extensively and with very fruitful results.

Autolysis is generally studied by the method first used by Salkowski, which depends upon the fact that the bacteria of putrefaction may be held in check by certain antiseptics that have relatively little injurious influence upon the enzymes. The common method of procedure is to grind up the organs or cells that are to be examined to a fine pulp, place the mass in flasks, after diluting with water, salt solution, or very dilute acid solution, and then add the antiseptic. Toluol, chloroform, and thymol are most commonly used, but comparative studies seem to show that of these toluol has the least depressing effect upon the autolytic processes. It is also possible to secure tissues in an aseptic condition and permit them to autolyze aseptically without the presence of antiseptics; the rate of autolysis under these conditions is more rapid than in antiseptic autolysis, but the practical difficulties are so great that it is employed but relatively little. Autolysis proceeds most rapidly if the material is kept at body temperature, but will go on slowly even at nearly the freezing-point, as shown by the slow "ripening" of meat in storage, which is an autolytic process. The presence of any substances that will impair or destroy ordinary proteolytic enzymes will prevent autolysis, *e.g.*, formalin, alcohol, bichlorid of mercury, etc. To determine the rate or amount of autolysis the usual method employed is to heat the autolyzing material to boiling at the close of the experiment, filter, and determine the proportion of the total nitrogen that is in a soluble, non-coagulable form; this figure can then be compared with the results obtained from con-

trol specimens that have been first heated to destroy the enzymes, and thus the amount of disintegration of the tissue proteins into soluble substances can be estimated. Another method, suitable for many kinds of studies, has been advocated by Wells and Benson; this consists in estimating the amount of changes in the freezing-point and the electrical conductivity of the autolyzing mixture, which are greatly modified during the course of the digestion because of the conversion of the large molecular complexes of protoplasm into smaller crystalloidal molecules that increase the conductivity and depress the freezing-point. The latter method is particularly advantageous where the amount of material available is limited, and where large numbers of determinations must be made for the plotting of curves.

Since the publication of Jacoby's paper awakened interest in the subject of autolysis, extensive investigations have been made by many workers, who have demonstrated that the property of autolysis is inherent in every cell, whether animal or vegetable, including not only the actively metabolizing cells of such organs as the liver, but even the stroma cells; and also unicellular organisms, such as yeasts and bacteria. However, the rate at which autolysis occurs in different sorts of cells varies greatly, such active cells as those of the liver disintegrating very rapidly as compared with stroma, muscle, and nerve cells. As commonly observed in experimental work, autolysis does not begin, or at least does not become appreciable in amount, during the first two or three hours after the tissue has been removed from the body; then the rate of proteid disintegration begins to increase rapidly, reaching a maximum from the twelfth to the twentieth hour (at body temperature), then subsiding until, after the forty-eighth hour, the daily increase is almost inappreciable. The intracellular proteolytic enzymes which accomplish this disintegration are not altogether like either pepsin or trypsin; they resemble the latter in carrying the digestion beyond the stage of peptones to their ultimate constituent amino-acids, but, like pepsin, for the most part they act best in a faintly acid medium, and are inhibited almost entirely by alkalies no stronger than 0.4 per cent. NaOH. The cleavage products that they produce from proteins differ from those of tryptic digestion in containing a much larger proportion of the nitrogen in forms simpler than the amino-acids, especially ammonia compounds; this extreme cleavage is probably the result not of one, but of several intracellular enzymes, including not only enzymes that decompose proteins into amino-acids, but also those that decompose the amino-acids into ammonia compounds (*deamidizing enzymes*). Probably as a result of this deamidizing process, organic acids, especially lactic, acetic, and butyric, are formed in considerable quantities.

As cells contain substances other than the proteins, the changes of cellular autolysis are by no means limited to proteolysis. Glycogen is split very quickly into glucose, which in turn is further disorganized. The intracellular fats are split by the lipase which every cell contains, so that free fatty acids may be found in autolyzing organs. Microscopically there may be found what seems to be an increase in the amount of fat in the cells, resembling the changes of fatty degeneration; but analysis shows that there is not an actual increase in fat, but rather a decrease, the fat microscopically observed being simply the result of the liberation of fats held normally in an unstable condition in the protoplasm of the living cell. Lecithin is also decomposed, yielding cholin. Reducing substances appear, and, as before mentioned, volatile fatty acids are produced. The nucleo-proteins are attacked early, causing the nuclei to lose their characteristic staining properties, and the nucleic acids which are liberated are decomposed by special enzymes, the *nucleases*, so that free purin bases appear; these in turn may be altered, adenin and guanin being changed into xanthin and hypoxanthin by the enzymes *adenase* and *guanase*.

AUTOLYSIS AS A PHYSIOLOGICAL PROCESS.—In view of the fact that every living cell, so far as known, is

provided with proteolytic enzymes, it would seem probable that these must be of importance to the cells in performing their normal functions, for it scarcely seems reasonable to contend that the cells are equipped with these enzymes solely for the purpose of acting as scavengers of the dead cells. Furthermore, we have ample reason to believe that the cells have need of proteolytic enzymes in order to be able to utilize the protein supplies brought in the blood, and perhaps also for the purpose of building up the cell proteins themselves. Therefore it seems very likely that the autolytic enzymes are simply the proteolytic enzymes that have to do with normal cellular metabolism, and that they act autolytically only when the cell is killed, or shut off from its supply of nourishment, or under other abnormal conditions, and there is some evidence in favor of this view. For example, Jacoby found that if he ligated off a portion of the liver of a dog, and let the animal live a few days, the necrotic tissue showed an accumulation of leucin, tyrosin, and other products of protein hydrolysis, which suggests that these same processes of hydrolysis are going on in the liver constantly, only the products of the hydrolysis are, under normal conditions, removed by the circulating blood as fast as formed. Furthermore, actively functioning tissues, such as the uterus and mammary gland in pregnancy, show much more active autolysis than do the same tissues when in the resting state; and Schlesinger found that autolysis is most rapid in newborn animals. Schryver found evidence that animals which had been fed on thyroid gland, which increases the protein metabolism, showed a more rapid autolysis of the liver than control animals; however, the writer has been unable to find any evidence that thyroid extract increases the rate of autolysis under experimental conditions. Nevertheless, in spite of this supportive evidence, it must be admitted that at the present time we are by no means certain that the enzymes that cause autolysis of dead tissues perform any part in normal metabolism, or, indeed, that these same enzymes really exist in the intact, normal cell in an active condition.

Another interesting problem is the manner in which the autolytic enzymes are kept from digesting the living cells, and why they attack only dead or injured cells; it will be noted that this question is much the same as the old problem of the defence of the gastro-intestinal mucosa from the enzymes of the digestive fluids. There are several observations that bear upon this point. One is that the blood serum has a powerful inhibitory action upon the autolytic processes, so that if a large excess of serum is present in proportion to the amount of cells, as in a serous exudate, autolysis may be held entirely in check. This inhibition seems to be due to specific antibodies present in the serum, which are readily destroyed by heat, by acids, and also by alkalis in any considerable concentration. As these antibodies are particularly susceptible to acids, the development of an acid reaction in an autolyzing area greatly facilitates the process, while, so long as the tissues are kept alkaline, autolysis is prevented. Furthermore, the autolytic enzymes, independent of any question of antibodies, with a few exceptions act much better in an acid than in an alkaline or neutral medium.* Therefore it may well be that in the living tissues, bathed with the normal quantities of constantly changing blood and lymph, the autolytic enzymes are held in check by the antibodies of these fluids; and at the same time the great neutralizing power of the blood plasma prevents the development of an acid reaction from any of the products of cellular metabolism. As soon as circulation is stopped by any cause, since the supply of antibodies is thus cut off, autolysis can begin after a latent period during which, presumably, the effect of the antibodies present is being exhausted; once autolysis is started, the formation of volatile fatty acids favors greatly the a-

tivity of the enzymes, and so the process soon begins to increase greatly in rapidity.

Another possible factor in the defence of the cells against their own enzymes is that to a certain degree the autolytic enzymes of each organ are specific for the cells of that organ (Jacoby). For example, liver extract will not digest lung tissue, or kidney, or spleen. Leucocytic enzymes, however, seem to be capable of splitting foreign proteins of all sorts. (The digestion of one cell by enzymes derived from some other cell is called *heterolysis*.) Still another reason that may be advanced to explain the attacking of a cell by its own enzymes immediately after its nourishment is shut off, is to be found in the conditions of chemical equilibrium. During life constant new supplies of proteins are being brought to the cell, and the products of proteolysis are carried away or oxidized as fast as formed; when circulation stops, the process of splitting goes on without the introduction of any new supplies of material, and hence the tissues are not replaced as fast as they are destroyed, and the products of their decomposition accumulate for lack of any means of destroying or removing them. There can be no question that the supply of food-stuffs is of essential importance in determining autolytic changes, for it has been found that bacteria and yeasts begin to undergo autolysis when they are taken out of nutrient media and placed in distilled water or salt solution. So long as the bacteria are supplied with nourishment, autolysis is not marked, but when nutrient material is lacking the autolytic decomposition is no longer repaired, and the bacteria disintegrate. Presumably the same rules apply to the individual cells of complex organisms.

Lastly, it must be considered that enzymes exist in the cell to greater or less extent in their inactive *zymogen* form, and are perhaps changed into the active form as needed, and inhibited or changed back again when their work is temporarily finished.

AUTOLYSIS IN PATHOLOGICAL CONDITIONS.—All absorption of dead or injured tissues, and of organic foreign bodies, seems to be accomplished by means of the digestive action of the enzymes of the cells and tissue fluids. We may distinguish between the digestion brought about by the enzymes of the digested tissue itself, or autolysis in the limited sense of the word, and digestion by enzymes from other cells or tissue fluids, or heterolysis, although in ordinary usage the word autolysis covers both processes. Heterolysis is accomplished particularly by the leucocytes, which contain enzymes capable of digesting not only leucocytic proteins but apparently every other sort of protein, from serum albumin to cat-gut ligatures. The heterolysis may be intracellular, in the case of substances engulfed by phagocytes; or extracellular, either by enzymes normally contained in the blood plasma and tissue fluids, or by enzymes liberated by the leucocytes and fixed tissue cells. On the death and dissolution of a cell the intracellular enzymes are released, but it is not known to what extent the enzymes may be secreted from intact living cells. So far as pathological processes show, the amount of liberation of enzymes from normal cells is very slight, if any; and the digestive enzymes present in the blood plasma seem to be very feeble, but this is perhaps because they are held in check by the antisubstances of the serum. Pathological autolysis and heterolysis, therefore, are brought about chiefly by enzymes liberated from dead or injured cells, and both these processes seem to take place in the softening of pathological tissues, etc. An infarct undergoes gradual absorption because the dead cells are digested by their intracellular enzymes, exactly as they are when the tissue is removed from the body and allowed to undergo experimental autolysis. In addition, in the case of the infarct, leucocytes wander in and disintegrate, and their liberated enzymes help in the process. It is because of the heterolysis by leucocytic enzymes that a septic infarct becomes softened so much more rapidly than does an aseptic infarct, and by comparing the rate of autolysis in these

* There are a few autolytic enzymes, notably those of the leucocytes and bone marrow (Opie), and an enzyme in the spleen (Hedin), that act best in a slightly alkaline medium.

two kinds of infarcts we see that cellular autolysis is a very slow process as compared with the heterolysis accomplished by leucocytes.

It is probable that the products of autolysis are toxic, and the aseptic febrile condition occurring in patients with large areas of aseptic necrosis, or with sterile hæmatomas, and sometimes called "ferment fever," may perhaps be the result of the absorption of the substances produced by the action of the autolytic enzymes. It is well known that albumoses and peptones are toxic, and it is quite probable that some of the other products of proteolysis are poisonous; and it has been repeatedly shown that they are hæmolytic. Some of the symptoms of suppuration, particularly the fever and chills, have been ascribed rather to the autolytic products than to the bacterial poisons, particularly as aseptic suppuration is accompanied by fever. In all conditions associated with autolysis albumoses may appear in the urine, and it is quite probable that they would cause more or less intoxication before being eliminated.

As specific instances of autolysis in pathological conditions may be mentioned the following:

Necrotic Areas and Exudates.—The processes that take place in a local area of necrosis must be fundamentally quite similar to those occurring in a corresponding piece of tissue kept in an incubator under aseptic conditions. The rate of the changes as actually observed is, however, very much slower in the case of the dead tissue within the living body, which is probably due to the inhibitory effect of the blood serum; indeed, if we add a large volume of blood serum to tissues placed in the flasks for experimental autolysis it will be found that the rate of autolysis is greatly lessened. In the case of very large areas of necrosis the central portions are found to undergo softening much faster than the peripheral, undoubtedly because removed from the inhibitory action of the serum. The disappearance of nuclear staining, which is the usual microscopic indication of necrosis, is probably due to the digestion of the nucleoproteins by the proteolytic enzymes and the nucleases, for if sterile pieces of tissue which have had their enzymes destroyed by heating are implanted into animals they are found to retain their nuclear staining for several weeks. The rate of autolysis under experimental conditions, as shown by the nuclear changes, is in decreasing order, as follows: Liver, epithelium of the convoluted tubules of the kidneys, spleen, pancreas, collecting tubules and glomerules of the kidney, alveolar and bronchial epithelium of the lung, thyroid epithelium, myocardium, voluntary muscle, squamous epithelium of the skin, cortical cells of the brain, connective-tissue cells, endothelium of blood-vessels.

If chemotactic substances are formed in a necrotic area the leucocytes that enter cause very rapid heterolysis. In *caseation*, for example, there is practically no autolysis, but if iodoform is injected the leucocytes that invade the area at once cause rapid softening, with the formation of "sterile pus."

Suppuration is an example of very rapid autolysis and heterolysis, particularly the latter brought about by the great number of leucocytes that are always present. As living cells do not undergo digestion, we do not get suppuration, no matter how many leucocytes there may be present, unless there is also present necrosis or some non-living protein material, such as fibrin, for the enzymes to attack; this is well illustrated by the absence of suppuration in erysipelas, in spite of extreme infiltration with leucocytes.

Exudates undergo autolysis, as Opie has pointed out, in direct proportion to the number of leucocytes, and in inverse proportion to the amount of serum. If the amount of serum is relatively very great, as in many forms of serous pleuritis, the antibodies of the serum hold the enzymes of the leucocytes in check, and there is little or no autolysis; but if the leucocytes are very abundant and the amount of serum small, then autolysis will occur. In this connection it should be recalled that

the enzymes of leucocytes are remarkable in acting best in an alkaline medium, so that it is not necessary for an acid reaction to be developed in order that they may become active.

Pneumonia.—The resolution of the exudate in lobar pneumonia is a striking example of autolysis by leucocytes, and its great rapidity undoubtedly depends upon the fact that the process occurs in the alveoli, and out of direct contact with the circulating blood and its antibodies. The important fact that in the resolution of pneumonia the alveolar walls escape digestion while the exudate is being taken away, is due to the normal resistance of living cells to digestive enzymes, which in this case is certainly at least partly due to the presence of abundant blood in the alveolar walls; in case the nutrition of a pneumonic area is cut off by thrombosis the autolytic changes then involve also the affected long tissue, resulting in purulent pneumonia, gangrenous softening, or abscess formation. As evidence of the autolytic nature of resolution we have the presence of albumoses and peptones in the sputum and urine of patients after the crisis of lobar pneumonia, and leucin and tyrosin have been found in pneumonic lungs.

Liver Degenerations.—In a number of pathological conditions of the liver, of which acute yellow atrophy is the type, autolytic destruction of the parenchymatous elements is the chief cause of the anatomical changes observed, and perhaps also of many of the clinical features. In acute yellow atrophy, for example, we have a rapid decrease in the size and weight of the liver because of disappearance of a large proportion of the hepatic cells, and in this condition leucin and tyrosin may be found in the urine, while in the blood, and especially in the liver itself, there may be found any and all of the products of proteolysis. Similar conditions exist in phosphorus poisoning, in the diffuse necrosis observed in the liver in cases of delayed chloroform poisoning, in some cases of puerperal eclampsia, and in certain infectious conditions with hepatic necrosis, especially in Weil's disease. It would seem that in these conditions we have the liver cells injured by some poison that stops the synthetic activities or kills the cells outright, but does not injure the autolytic enzymes, so that the latter accomplish the disintegration of the cells. Possibly the reason that the liver is peculiarly liable to such *intra vitam* autolytic destruction lies in the fact that it is notably possessed of the most active autolytic enzymes.

Post-mortem Changes.—These are undoubtedly due to two factors, bacterial action and autolysis. Under ordinary conditions the former effect is so conspicuous that autolysis is not prominent, but there are instances in which post-mortem decomposition is purely autolytic. The best example is furnished by the disintegration of the fetus that is retained within the body of the mother after its death from whatever cause; the maceration of the tissues, and the disintegration of the viscera, are the result of autolytic processes. In the "ripening" of meat kept at low temperature to prevent bacterial action we have a case of slowly continued autolysis, and even in fish and meat cured with brine, autolysis seems to take place in spite of the strength of the salt solution used. The softening of the muscles after rigor mortis is probably also the result of autolytic decomposition of the clotted muscle proteins. The microscopic changes that occur in tissues undergoing post-mortem decomposition are readily explained as the effect of autolytic attack upon the cellular structures, and are, in fact, quite the same as those occurring in necrotic areas within the living body.

Tumors.—As necrosis is a prominent feature of malignant tumors, autolysis results in their softening and breaking down, showing that tumor cells possess autolytic enzymes as well as the normal cells of the body. It is possible that the products of this extensive autolysis that occurs in tumors have an important influence in the production of cancer cachexia. Extracts of malignant tumors have a decided hæmolytic property, which very probably is due to these products of autolysis, and their

absorption into the blood may have to do with the anemia of cancer patients. On account of this hæmolytic property, blood-stained exudates produced by malignant growths in the serous cavities usually will be found to owe their color to hæmoglobin rather than to red corpuscles. The action of radium and x-rays upon malignant growths has been ascribed to the effect of these agencies upon the autolytic enzymes; Neuberg found that although most enzymes are destroyed or inhibited by radium emanations, autolytic enzymes form an exception, for cancer tissue exposed to radium rays undergoes autolysis faster than control specimens. Products of protein hydrolysis may be found in tumors on account of their autolytic disintegration.

Leukæmia.—The abundant elimination of uric acid and other purin bodies in leukæmia is probably due to the autolysis of leucocytes that occurs in this disease. Leucocytes obtained from cases of myeloid leukæmia show very active autolytic properties, which are comparatively slight in leucocytes from lymphatic leukæmia. Corresponding with this, the evidences of autolytic processes are much more prominent in cases of myelogenous leukæmia. It seems quite probable that an important factor in this autolysis is that the proportion of leucocytes to serum in the circulating blood is greatly raised, so that the antibodies present in the blood are inadequate in amount to hold the leucocytic enzymes in check, as normally occurs. It has been found experimentally that leukæmic organs, especially the spleen, undergo autolysis more completely and more rapidly than do normal organs. The effect of x-rays upon this disease is possibly the result of their action upon the intracellular enzymes, as in the case of cancer.

AUTOLYSIS OF BACTERIA.—As previously mentioned, bacterial cells present no exception to the general rule that all living cells contain autolytic enzymes. This property of bacteria is shown as soon as they are removed from culture media and placed in non-nutrient fluids, such as water or salt solution; then the bacteria begin to undergo self-digestion in a few hours, as if their enzymes attacked the bacterial cells when there is nothing else for them to act upon. Likewise, if bacterial cells are placed in antiseptics that do not destroy the autolytic enzymes, such as toluol and chloroform, autolytic disintegration begins to take place at once. In this way it has been possible to liberate from bacterial cells the poisonous substances that they contain, the *endotoxins*. It is probable that such bacteria as owe their pathogenic properties to endotoxins produce their effects only when these are released through disintegration of the bacterial cells by autolysis or when the bacteria are digested by the enzymes of the infected organism. On this account it is possible for a perfectly immunized animal to be killed by the injection of large numbers of such bacteria (e.g., typhoid, colon, cholera) through overwhelming with great quantities of endotoxins, even when every bacterium has been killed by the protective agencies of the animal, since when the bacteria are killed the endotoxins are liberated by digestion of the dead bacterial cells.

Part of the tissue digestion that occurs in infected areas may be due to the action of enzymes liberated by the infecting bacteria, but as compared with the effect produced by the leucocytes this influence is probably negligible. Certain of the products of autolysis of tissues are antiseptic and it is possible that a certain degree of resistance is conferred by these substances in local infections accompanied by tissue destruction. Conradi believes that it is the accumulation of these antiseptic products of the autolysis of bacteria that accounts for the gradual dying out of bacteria grown on artificial media. It is quite possible that bacterial toxins may be destroyed by autolytic enzymes, for it is known that toxins are attacked by proteolytic enzymes.

H. Gideon Wells.

The Bibliography of this subject is given by Salkowski, *Deutsche Klinik*, 1903 (11), 147; A. Oswald, *Biochemisches Centralblatt*, 1905 (3), 365; and in the chapter on Autolysis, in Wells' "Chemical Pathology."

BACILLI CARRIERS.—It has been known for several years that persons convalescent from certain acute infectious diseases of known etiology may thereafter carry and excrete the exciting organisms from their bodies for a variable length of time. Almost coincidentally it was discovered that not only those who have suffered from a specific infectious disease harbor the causative organisms, but also others who have been in direct contact with either such patient or the infectious material. These persons are apparently in normal health, or do not show any symptoms of the specific disease. Recently the general term of "bacilli carriers" or "bacteria carriers" has been applied to such persons.

It is difficult to define strictly what constitutes a true bacilli carrier. The term is subject to broad interpretation, but, as commonly understood at the present time, certain restrictions must be made to fix proper limitations. Therefore we may say provisionally that a bacilli carrier is one who, while apparently in good health, or at least not showing any symptoms of a particular specific infectious disease, is harboring and excreting certain pathogenic organisms of such virulence that, when transmitted directly or indirectly to a second person, or to an experimental animal, they are capable of causing the infectious disease in question. The carrier may or may not have given a history of a previous attack of the disease.

The first observations in this direction were made in connection with epidemics of cholera, diphtheria, and cerebrospinal meningitis. This list of infectious diseases is being constantly added to as investigations continue along this line.

Asiatic Cholera.—It has been found by a number of workers in epidemiology that in cholera epidemics there are healthy persons in the infected district who carry virulent vibrios in their intestines, but who are insusceptible to the disease. Abel and Claussen report an extreme case in which they found cholera vibrios in the dejecta of fourteen out of seventeen persons belonging to families wherein there were cholera patients. In some instances the organisms persisted as long as fourteen days. In the Hamburg epidemic there were reported twenty-eight cases of healthy persons with normal stools containing cholera vibrios. Cholera vibrios are usually found in the dejecta of patients for only a few days, but Kolle found virulent organisms in the stools of convalescents, up to forty-eight days. A case has been reported in which the organism was found one hundred and twenty days after the attack.

It is evident from the above that the dissemination of cholera comes about not only through contamination of water, food, etc., from the discharges of those acutely ill of the disease, but also from the discharges of certain convalescents and healthy "carriers," who may play an important rôle in spreading the disease.

Diphtheria.—As early as 1894 Park and Beebe examined the throats of three hundred and thirty healthy persons. In eight subjects virulent diphtheria bacilli were found, and two of those afterward developed the disease; twenty-four subjects in this series showed non-virulent or attenuated forms of the organism. In further studies upon the persistence of the virulent organisms in the throats of convalescents a large series of consecutive cases were examined. It was found that in approximately fifty per cent. of the cases the bacilli disappeared within three days after loss of the pseudo-membrane. A majority of the remaining patients showed the disappearance of the organisms in rapidly decreasing numbers over the following two weeks. But in a few cases the bacilli persisted from the fourth to the ninth week. Park later reported the case of a patient who carried fully virulent organisms for eight months. Fripp reported a case in which the virulent organisms persisted for twenty-two months.

Recently Pennington published the results of his examination of the throats of a large number of well school children in Philadelphia. The summary of his

findings is very interesting in this connection. He found that approximately ten per cent. of these children harbored in their throats bacilli which corresponded morphologically with the organism of diphtheria. One-half of these organisms were without effect upon guinea-pigs. About thirty per cent. behaved like attenuated forms, and fourteen per cent. killed the animals with a fair degree of promptness.

In the examination of the throats of well persons in contact with diphtheria patients, Kober found that eight per cent. carried virulent bacilli. It is generally considered that the bacilli found in well persons recently exposed are more likely to be virulent than others.

Many more studies along these lines have been made which confirm the findings just mentioned. All these observations point to the fact that not only convalescents but apparently well individuals may serve as carriers of virulent diphtheria bacilli, and under favorable conditions can infect others.

Cerebrospinal Meningitis.—The *Diplococcus intracellularis meningitidis* of Weichselbaum is another organism which is found in normal persons. In the examination of twenty-seven healthy persons Schiff found in the nasal secretions of seven an intracellular diplococcus; in three cases of this group Weichselbaum identified the organisms as being meningococci. Weichselbaum and Ghon isolated the same organism from three persons who had been in contact with the disease. Goodwin and von Sholly found the meningococcus present in about ten per cent. of the people who were in close contact with patients suffering from the disease. Others have found the meningococcus in the throat and nasal cavities of healthy persons, during an epidemic of meningitis. The organism may persist a considerable length of time in convalescents. Goodwin found the organism persisting sixty-seven days after the onset of the disease.

Evidence seems to indicate that cerebrospinal meningitis is not highly contagious. Those who contract the disease usually have had their general resistance lowered by unhygienic environment, hardships, exposure, etc. Individual susceptibility is an important factor. The organism may set up an acute rhinitis without further invasion or harm. This partly explains how the infection may be carried and distributed, as it is well known that the organism possesses a low degree of vitality; it is rapidly killed by drying, sunlight, etc. Therefore, immediate or mediate transmission of the infected secretions from one person to another seems to be necessary in most cases. Dwelling infections are not proved. The influence of "bacteria carriers" in the spreading of this disease may account for the outbreak and confinement to one family, small area in a community, or a single regiment. Probably certain outbreaks of cerebrospinal meningitis in barracks may have their origin from "bacteria carriers." Several instances are on record which would indicate that this is the case.

Influenza.—The influenza bacilli may be harbored in the respiratory and nasal passages of many well persons, who seem immune to their action. They may also occur as a secondary infection in many other conditions. Williams quite early observed them in sputum from pulmonary tuberculosis; they were present in great numbers in a large portion of the cases, and in some cases in almost pure cultures. Moreover, they were found not only during the winter but also during the summer, when no influenza was known to be prevalent. There is no doubt that tuberculous patients act as influenza bacilli carriers. Also certain healthy persons play a similar rôle.

Typhoid Fever.—Perhaps the most thorough studies upon "bacilli carriers" have been carried out in connection with typhoid fever. Several extensive reports have recently appeared upon this subject. Although these conditions have been recognized only within the last few years, the investigations promise to throw much light upon certain outbreaks of the disease of obscure origin. At the present time considerable work

upon this phase of the epidemiology of typhoid is being pursued both in this country and abroad.

It has been known for a number of years that typhoid patients and convalescents might carry pure cultures of the bacillus in the bladder for an indefinite period of time. Petruschky in 1898 reported typhoid bacilli in the urine of convalescents, as long as two months after the attack. Richardson soon after mentioned a case, observed by Cushing, of a man who had had typhoid fever five years previously, but returned to the hospital for treatment of cystitis. Bacteriological examination revealed a pure culture of typhoid bacilli, which would indicate that the infection had been carried five years, following the typhoid-fever attack.

Since these early reported cases it has been well confirmed that in some cases typhoid convalescents carry the bacilli a variable length of time as bladder infections, and become a constant source of further infection by discharging the organisms in the outer world. Donitz and others have reported cases which fully support the claim that infections can originate from such a source.

As early as 1902 Frosch suggested that convalescents from typhoid fever in some instances might carry the bacilli in their bodies as saprophytes, and their dejecta might give rise to new infections. In this way the mystery of "typhoid houses" or "typhoid localities" might be explained. Sound persons might be "bacilli carriers" and be the source of infection.

Drigalski and Conradi in the same year reported the isolation of typhoid organisms from the dejecta of four healthy persons who had been in contact with cases of the disease. Drigalski in 1904 reported a case in which the organisms were observed for nine months in the stools. The next year Lentz and others confirmed the supposition of Frosch and the findings of Drigalski and others. Since then many more contributions have been made on the subject which give further support to the views concerning "typhoid-bacilli carriers."

Lentz (1905), in making an extensive review of the results obtained at several laboratory stations engaged in the investigations of typhoid fever, states that out of a large number of examinations ninety-eight chronic "bacilli carriers" were found. At one station it was found that about four per cent. of the cases examined became bacilli carriers. In one instance Lentz found that out of twenty-two carriers sixteen were women. He observed that a definite relationship existed between gall-stone disease and "bacilli carriers," as the two conditions might be associated, and suggested that gall-bladder infections might give rise to the typhoid bacilli in the feces.

Neiter has called attention to the influence of bacilli carriers in causing institutional epidemics. In a certain German insane asylum were found thirteen "bacilli carriers," all women. Friedel traced the cause of a series of typhoid outbreaks in the institution, to a "bacilli carrier" who was a helper in the kitchen of the asylum.

Kayser reported small outbreaks of typhoid fever which could be traced to the milk in use. In two instances the milk was traced back to the respective dairies. In each case a "bacilli carrier" was found in connection with the dairy, proof being furnished by the isolation of typhoid bacilli from the feces. Kossel describes a similar outbreak which had its origin from milk supplied from a certain dairy. Upon investigation it was found that one of the laborers was a "bacilli carrier," although he was not aware that he ever had the disease. He was removed from the dairy work, with the result that no more cases developed from the milk supply. Later, he returned to the work and a second outbreak followed. These examples prove very instructive, as they show the danger of employing "bacilli carriers" as workers about such places.

Soper records a most interesting and instructive case of a typhoid-bacilli carrier. He was called upon to investigate a household epidemic of typhoid fever, where, in close succession, six out of eleven were stricken with the disease. The water and food supplies were fully

examined, with the result that they could be excluded as sources of infection. Finally, suspicion was directed to a cook who had been employed by the family shortly before the outbreak of the disease. She left shortly afterward. Soper succeeded in locating the cook again, but was unable to derive any useful information from her. She was a woman of apparently good health, about forty years of age, of Irish descent, single, and had no knowledge of ever having had typhoid fever. She refused to give further information concerning her past life, and the investigator therefore found it necessary to look up her past history. During the previous ten years it was possible to trace her whereabouts with the exception of two years. It was found that in the time accounted for she had been employed in eight families, and in seven of these typhoid fever had followed her. She had always escaped the epidemics herself. In all, twenty-six cases and one death occurred in the series of outbreaks. The last position she held was with a family in New York City, and the outbreak in this instance was followed by the only fatality. Soper called the attention of the Department of Health to the cook, who was suspected of being a chronic carrier and a menace to public health. She was placed in the Detention Hospital March 19th, 1907, where she has been under constant observation ever since (January, 1908). Bacteriological examinations carried out, under the directions of Dr. Park of the Research Laboratory, by Goodwin and Noble showed that the urine was free from typhoid bacilli, but the feces were rich with the organisms. The examinations have been continued almost a year, with the results that with few exceptions typhoid bacilli have always been present. This establishes a case of a constant bacilli carrier. The blood showed a positive Widal test early in the course of the examination. This side of the investigation has not been followed along with the feces examination, owing to the vigorous protests of the carrier. It is not necessary to dwell upon this case, further than to call attention to the havoc which a carrier can produce when coming in direct contact with the food supply of non-immune individuals.

Klingler divides typhoid-bacilli carriers into two groups: (a) those who have had typhoid fever at some time or other, and (b) those who have no knowledge of ever having had the disease. In a series of twenty-three cases which came under his observation, he found that six men and five women fell in the first group, while in the second group there were three men and nine women.

The discharge of typhoid bacilli in the feces of carriers may be quite irregular in some cases, while regular in others. This seems to depend on temporary conditions in the intestinal tract. It has been observed that sometimes the discharge of bacilli will suddenly stop without recurrence. Also there may be all degrees of gradation as to the length of time the bacilli continue to be present in the feces after the acute attack. They may not be found at all after convalescence, or they may be present weeks, months, or years thereafter. Lentz mentions one case in which the organisms were present forty-two years after the attack. From this we can easily see that there may be no age limit. Klingler in his series found bacilli carriers between the ages of eighteen months and sixty years. The infant cases may have been contracted through the mother.

The focus of infection is generally considered to be in either the gall-bladder, chronic ulcers of the intestines, or the normal intestinal tract. Wasserman and Citron are of the opinion that a local immunity exists in the gall-bladder and intestinal wall of the carrier, which protects the body from general infection. A number of workers report that there is no raising in value of the specific agglutinin, nor in specific bactericidal substances; but others have reported that such substances are increased. It is desirable that more work be done in regard to these particular points.

Medicinal treatment or immunization, according to

Forster and Kayser, seems so far to have been attended by practically no favorable results, in the intestinal cases. But in the bladder infections Richardson found urotropin very efficacious. The use of this drug might be of service in the gall-bladder infections. A successful use of urotropin in gall-bladder infection has recently been reported from the Johns Hopkins Hospital.

When the infection in these cases can be localized by such evidence as concomitant gall-stone disease, operative means may in some cases lead to cure. Dehler recently (1907) operated upon a patient who was a chronic bacilli carrier, with the purpose of relieving the condition. Perhaps this is the first operation on record which was undertaken for the cure of a typhoid carrier. The patient, an insane woman, had infected a number of persons before it was discovered that she was a carrier. Previous to the operation typhoid bacilli were found in the feces in thirty-seven out of thirty-nine examinations. The operation consisted in making a section, freeing the gall-bladder from adhesions, opening it, and removing the gallstones, then giving free drainage for some time. The patient made an uneventful recovery, and with the exception of once shortly after the operation, the stools have since been free from typhoid bacilli.

Later on Dehler operated upon a second patient who was a bacilli carrier, and removed a few small stones from the gall-bladder. Subsequent examinations of the feces showed the absence of typhoid bacilli. In the same communication he reported that the dejecta of the previous case still remained free from typhoid organisms. Both patients showed an improvement in their general condition. Dehler is of the opinion that operative means are justifiable in those cases in which no relief from the condition can be brought about by medication or immunization.

A number of cases have been reported in which the dejecta of chronic carriers have shown a mixed infection of the paratyphoid with the typhoid bacillus. Also paratyphoid bacilli carriers have been reported by Gaetgens and others.

Bacillary Dysentery.—As compared to typhoid fever, a limited amount of work has been done which will throw light upon the subject of bacilli carriers among convalescents from dysentery or of healthy carriers. But, taking up the closer study of certain epidemics of this disease, it seems possible that there are carriers in some instances. However, the investigations of Shiga, Flexner, Goodwin, and others, carried out in a large number of cases, have failed to show the presence of *B. dysenteriae* in normal stools.

In this disease, as in those discussed previously, the so-called latent types apparently may be a means of spreading the infection. Park is of the opinion that paratyphoid bacilli are distributed by carriers and may in some cases give rise to epidemics. Duval reported that he had found in two instances the *B. paratyphoid* in the normal stool of milk-fed infants. Collins also found a few cases in the normal stools of babies.

Gonorrhœa.—Many of the so-called cases of chronic gonorrhœa may be considered in the sense of being gonococci carriers. A certain percentage of the so-called chronic or latent cases do not show any clinical manifestations after a certain length of time following the acute infection. Yet these persons are quite capable of infecting others, and there seems to be no decrease in the virulence of the organism. Moreover, the person is subject to superinfection from other sources with acute clinical symptoms following. Apparently there is no limit to the time a man may carry the infection in chronic cases. Park mentions a case in which the organisms were abundantly present after an exposure dating back twenty years.

Another class of carriers may be those who have experienced slight if any clinical symptoms primarily, but who carry the organisms and are able to infect others.

Other Infectious Diseases.—Pneumococci and streptococci are quite frequently found in the throats and air passages of normal persons. While these organisms are

nearly as virulent to susceptible animals as when obtained from diseased cases, we are not yet certain whether they are as capable of producing disease in man. Many cases of pneumonia are undoubtedly due to autoinfection.

Concerning the tubercle bacillus we need further investigation. There may be certain persons who may harbor the bacilli and still give no evidence of any pathological condition caused by this organism. But this supposition seems to be improbable.

Bacilli carriers, or bacteria carriers, as stated, are a constant menace to public health, when allowed unrestricted freedom. It is imperative that such cases be recognized if possible, and the necessary steps taken, so far as is feasible, to combat the condition, or to prevent the spread of the disease by prophylactic means.

Patients recovering from these diseases should be thoroughly examined before being discharged in order to ascertain whether or not they are free from virulent organisms. Medicinal treatment, immunization, or surgical intervention may relieve certain cases, but when these means are not applicable it may be necessary to quarantine the patient. In all cases in which the dejecta carry infectious organisms complete sterilization should be employed. In safeguarding a water supply these bacilli carriers must always be kept in view.

When investigating the origin of an outbreak of an infectious disease, it is always important to bear in mind the possibility of a bacteria carrier as the source.

L. W. Famulener.

BACTERIOLOGICAL TECHNIQUE.—The methods for the artificial cultivation of bacteria are of fundamental importance in bacteriology, and for that reason deserve very careful consideration. Nutrient media of various kinds are used, but the three most commonly employed are bouillon, gelatin, and agar. These in turn may be variously modified as the needs of the work may require. In addition, other media are used, such as blood, serum, exudates, eggs, urine, milk, potatoes, and the like. These will be severally considered.

BOUILLON.—To prepare beef tea, or bouillon as it is called, 500 gm. of lean, chopped beef (Hamburger steak) are placed in a suitable enamelled vessel or in a one-and-a-half-litre flask and 1,000 c.c. of ordinary tap water are added, and the whole is thoroughly mixed. This may now be set aside in an ice-box for twenty-four hours so as to bring the soluble constituents into solution; or, what is preferable, it may be placed in a water-bath and warmed at a temperature not exceeding 60° C. for an hour. In this way the nutrient substances are dissolved out and much time is saved. It is not desirable at this point to heat the fluid above the temperature given, inasmuch as that would lead to the coagulation of the albuminous constituents, which, if they are allowed to remain in solution, will facilitate the subsequent clarification of the medium. When the digestion is completed, whether carried out at a low temperature or in the water-bath, the liquid is strained through well-washed, starch-free muslin, or the juice may be expressed by means of a meat press. The liquid thus obtained is of a dark red appearance, due to the presence of hæmoglobin.

One thousand cubic centimetres of the meat extract are then placed in a clean flask or vessel, and 10 gm. of dry, powdered peptone (Witte's) and 5 gm. of common salt are added and the whole is then warmed at about 55° to 60° C. till the peptone has dissolved. The next step is to render the medium suitably alkaline, since bacteria as a rule require a slightly alkaline soil. This manipulation requires special care, for, if improperly done, the finished product may be cloudy, or may even have a deposit, or may even be unfit for the growth of bacteria. The clouding and the formation of a precipitate can be avoided by boiling the meat extract after adding just enough alkali to neutralize the fluid. For this purpose 5 c.c. of normal sodium hydrate (four-per-cent. solution) are added to the litre of meat extract. This amount is usually sufficient to make the extract neutral to litmus. The

liquid is then heated in a boiling water-bath or over a free flame for about fifteen minutes, after which it is filtered through a moist plaited filter and allowed to cool to about 50° C. As stated, bacteria thrive best when the medium is slightly alkaline. Hence 10 c.c. of the normal sodium hydrate are now added to impart the desired alkalinity, after which the liquid is again boiled for twenty to thirty minutes, and finally filtered through moist paper.

Inasmuch as considerable water is usually lost by vaporization during the preparation of the medium, it is advisable either to indicate the volume at the beginning of the operation by a suitable mark on the vessel, or, better, to take the weight of the fluid before and after heating. The difference in the volume or weight is finally made up by the addition of the corresponding amount of distilled water. The finished bouillon should make up to the original volume of meat extract, that is, 1,000 c.c.

The beef tea thus prepared is now filled into tubes or into flasks, as the case may be, and sterilized by steam. This process will be described later. It is hardly necessary to add that the bouillon after being tubed and sterilized should be perfectly clear, without a deposit, and should have a slight alkaline reaction.

For cultivating the gonococcus Thalmann recommends using the ordinary bouillon, to which has been added two-thirds to three-fourths of the amount of alkali necessary to make it neutral to phenolphthalein.

Sugar-free Bouillon.—The bouillon as just prepared always contains some sugar derived from the muscle tissue employed. For many purposes this sugar content is undesirable, and must be removed in some way. One procedure is to allow the meat extract to ferment at a low temperature, 10° to 15° C., for two days. Another is to place the meat extract at 37° C. for twenty-four hours. Neither one of these methods will give results which can be relied upon. The best procedure is to add to the meat extract a rich fluid culture of some acid-producing organism, such as *Bacillus coli* (Smith), or *B. lactis aerogenes* (Durham), and then set it aside to ferment at 37° C. for twenty-four hours or longer. The frothy liquid is then carefully neutralized by the addition of normal sodium hydrate, peptone and salt added, then boiled, cooled, and rendered alkaline according to the directions given under the preparation of bouillon. The sugar-free bouillon thus prepared does not contain indol, as might at first be supposed. It is preferable to the Dunham peptone solution mentioned below for testing for the presence of indol, since a good reaction is given in sixteen hours, whereas the cultures in Dunham's solution often require several days before giving a positive test.

Martin's Bouillon.—The thoroughly mixed meat suspension (500 gm. of chopped beef and 1,000 c.c. of water) is set aside at about 37° C. for twenty hours so as to destroy the sugar normally present. The liquid is then strained through well-washed muslin, and to 1,000 c.c. of the filtrate 5 gm. of common salt are added, after which the liquid is neutralized and finally rendered alkaline by the addition of 7 c.c. of normal alkali per litre of bouillon. Ordinary peptone is not added, inasmuch as it is likely to contain sugar. Instead, Martin adds to this bouillon an equal volume of a rich peptone solution made by digesting the stomach of a pig. This latter solution is prepared as follows: A pig's stomach is cleaned and cut up into small pieces, and to 200 gm. of this finely divided tissue 1,000 c.c. of water and 10 c.c. of concentrated hydrochloric acid are added and the mixture is set aside at 50° C. for about twelve hours. The digested fluid is then decanted through a filter of absorbent cotton and the strongly acid reaction is reduced by the addition of 25 c.c. of a sixteen-per-cent. solution of sodium hydrate. The liquid is then carefully neutralized, after which it is rendered alkaline by the addition of 7 c.c. of normal sodium hydrate per litre. The mixture of equal volumes of the sugar-free bouillon and the peptone solution is heated, filtered, and tubed or placed in flasks.

Peckham's Bouillon.—This is made by taking finely chopped beef, which must be as old as it can be obtained

in order that it may be free from muscle sugar, and adding 225 gm. of it to 500 c.c. of water. The mixture is rendered slightly alkaline with sodium carbonate, after which it is placed in a water-bath at 40° C., and 4 gm. of trypsin are added. After digesting for an hour the fluid is again rendered alkaline with sodium carbonate. In from one to one and a half hours the digestion should be arrested, otherwise traces of indol may be detected. At the end of this period the mixture is boiled and strained through gauze and filtered cold through wet filter paper to remove the fat. Five grams of salt and enough water to make up to one litre are then added. The acidity of the clear straw-colored filtrate is then reduced to the desired point. The most suitable reaction for the development of colon and like bacilli is when the medium contains such an amount of free acid as to require from 20 to 30 c.c. per litre of a decinormal sodium-hydrate solution to bring it to a point neutral to phenolphthalein.

Artificial digestion of muscle tissue by means of pepsin and trypsin is resorted to in the preparation of Deycke's agar.

Dunham's Peptone Solution.—This is prepared by dissolving 10 gm. of Witte's peptone and 5 gm. of common salt in 1,000 c.c. of ordinary tap water. The solution is then tubed and sterilized by steam. This medium is used to detect the formation of indol by bacteria, but inasmuch as many organisms fail to grow in it and others require several days before giving a reaction, it has not been found to be as suitable as the sugar-free bouillon given above.

Glucose Bouillon.—This is used to test for acid and gas production. It is made by adding to the ordinary bouillon, or better to that which is sugar-free, one or two per cent. of glucose. The two-per-cent. solution is most commonly employed. The sterilization of sugar-containing media by steam requires special care to prevent oxidation of the carbohydrate present. As a rule the steaming should not exceed ten or fifteen minutes each day on three successive days. Instead of glucose other carbohydrates, such as lactose, maltose, saccharose, dextrin, etc., may be added to the bouillon in one- or two-per-cent. concentration.

Mannite-peptone Bouillon.—The alcohol mannite is added to sugar-free bouillon in sufficient quantity to give a one-per-cent. concentration. This medium is especially useful in differentiating organisms which otherwise closely resemble each other. For example, the different varieties of dysentery bacilli may be separated, since certain ones ferment mannite, while others do not.

Glycerin Bouillon.—This is especially used for cultivating the tubercle bacillus. It is made by adding five per cent. of glycerin to the ordinary bouillon. The mixture is then tubed and sterilized in the usual way.

Carbolic Bouillon.—This is made so as to contain 0.1 per cent. of carbolic acid. One gram of acid may be added to one litre of bouillon. The better procedure is to add 1 c.c. of a one-per-cent. carbolic acid to 9 c.c. of bouillon. It is advisable to incubate the tubes for several days so as to eliminate any possible contamination. The medium is useful for examining water for the colon bacillus, especially when the bacterial contents are very high. The presence of the antiseptic serves to check or prevent the growth of many organisms which would otherwise develop. It should be borne in mind that weak colon and typhoid bacilli are likewise restrained.

The tubes after inoculation with the water are incubated for twenty-four hours at 38° C., after which lactose litmus agar plates are made, which are then examined for red colonies. Of course all red colonies are not to be regarded without further study as the colon bacillus.

Parietti's Bouillon.—A mixture of carbolic acid and hydrochloric acid is first prepared by adding 4 c.c. of the latter to 100 c.c. of a five-per-cent. carbolic solution. This solution after standing a few days is added in portions of 0.1, 0.2, 0.3 c.c. to portions of 10 c.c. each of sterile bouillon.

Nitrate Bouillon.—The Laboratory Committee of the American Public Health Association recommends that this medium be prepared by dissolving 1 gm. peptone in one litre of tap water (ammonia-free), and then add 2 gms. of nitrite-free potassium nitrate. Ten c.c. of the medium are placed in test tubes and sterilized in the usual manner. It is best to prepare the medium fresh before using.

Calcium-salt Bouillon.—Bolduan found that the addition of certain calcium salts to plain broth gave a medium nearly equivalent to those containing serum, or ascitic fluid for the cultivation of the pneumococcus, meningococcus, etc. It has the advantage of being easily and rapidly prepared. Calcium chloride can be used in solution of 1 to 2,000 in plain broth, while calcium carbonate (marble) or calcium sulphate (gypsum) is broken into small pieces, washed with water, added to broth in test tubes, and sterilized in the regular manner. Pneumococci as a rule grow readily upon this medium, live approximately as long as upon ascitic broth, and retain their virulence equally well. Hiss, working independently of Bolduan, discovered the same advantages of calcium broth when cultivating the above-mentioned organisms, his publication appearing later.

MacConkey's Bile-salt Bouillon.—Bile salts and various sugars enter into this medium. A stock solution may be prepared without sugar, then the sugar may be added as desired. This solution is prepared by dissolving 20 gm. Witte's peptone in 1,000 c.c. distilled water heated to 60° C., then to this add 5 gm. sodium taurocholate (commercial product). For the bouillon add one-half per cent. of a freshly prepared one-per-cent. solution of neutral red, and the sugar desired. If glucose is used, one-half per cent. is added; in the case of other sugars, one per cent. The medium is sterilized in a steam sterilizer at 100° C. on three consecutive days. Care must be exercised in order not to overheat and split the constituents in sterilizing. These media are especially applicable in the differentiation of intestinal bacteria. The formation of both acid and gas may be observed if the organisms under cultivation possess such properties.

Colored Bouillon.—Various coloring agents are added to the nutritive media in order to bring out the acid-producing or the reducing properties of bacteria. The substances which are most commonly used for this purpose are litmus, neutral red, fuchsin, safranin, and sodium indigo sulphate. The first two are particularly useful, and are prepared the same as the corresponding agar or gelatin media, which see.

GELATIN.—The ordinary nutrient gelatin is really nothing more than bouillon to which ten per cent. of gelatin has been added so as to impart solidity with the additional advantage that the medium is transparent. The method of preparation is as follows: To 1,000 c.c. of the meat extract, prepared according to the directions given under bouillon, 100 gm. of the best sheet gelatin are added; likewise 10 gm. of Witte's peptone and 5 gm. of common salt. The whole is then warmed in a water-bath at 60° C. until the gelatin has passed into solution. The liquid is then neutralized and enough alkali added in excess so as to impart a suitable alkalinity. As ordinarily prepared the nutrient gelatin requires from 30 to 35 c.c. of normal alkali to effect neutralization. An additional 10 c.c. will give the desired alkalinity. Hence 40 c.c. of the normal alkali may be added at once and the liquid tested with litmus paper. If the liquid is not distinctly alkaline more of the reagent may be added until the desired alkalinity is obtained. The method of standardizing media by means of phenolphthalein will be given later.

When the proper amount of alkali has been added to the gelatin solution the latter is then placed in a water-bath, the water of which is then raised to the boiling temperature. The gelatin is kept immersed in the actively boiling water for about three-quarters of an hour. Prolonged heating or sterilization at high temperature (autoclave) lowers the solidifying point of gelatin;

therefore this must be avoided, since it impairs the medium. The albuminous constituents of the meat extract coagulate in flakes, and at the same time clarify the liquid so that on subsequent filtration the gelatin will be perfectly clear. In case the coagulation of the albumin results in minute particles, which cannot be readily removed by filtration through paper, egg-albumin may be added and precipitated by again heating. This is brought about by allowing the medium to cool down to 60° C. and to each litre add the whites of two eggs, then thoroughly mix by stirring. Gradually bring the temperature up near the boiling-point, without stirring, and keep there about fifteen minutes. A heavy coagulum results, the greater part of which will rise to the surface. This may be removed by straining through several thicknesses of cheese cloth or a layer of absorbent cotton placed in a funnel. The gelatin is then filtered through a plaited filter, which should, however, be first warmed by passing through it several hundred cubic centimetres of boiling water. If the paper and funnel are sufficiently warmed in this way there is no likelihood of the gelatin solidifying on the filter. The filtered gelatin should be perfectly clear, should possess a slight alkaline reaction, and should solidify when cooled under running tap water. If it meets these requirements it is then filled into sterile tubes to a depth of one and a half to two inches, and finally the tubes are sterilized by steaming for a quarter of an hour on each of three consecutive days.

Whenever nutrient gelatin is mentioned in bacteriological work it is understood to be a ten-per-cent. solution. This medium melts at about 23° C. That is warm summer temperature, and for that reason it is sometimes advisable to add more gelatin to the preparation in order to make it more solid. A twelve- or even a fifteen-per-cent. solution of gelatin is used under these conditions. Again, at other times it is desirable to employ a gelatin which is relatively quite soft, and in that case a five- or eight-per-cent. solution may be made use of. Obviously the amount of alkali necessary to neutralize such media will vary from that required for the ordinary gelatin. The great value of the gelatin medium lies in the fact that it can be readily melted and again solidified, and in its transparency. Moreover, many bacteria give rise to soluble ferments or enzymes which peptonize or liquefy the gelatin, whereas others are not able to do this. It becomes possible therefore to divide bacteria into two large groups, according as to whether they liquefy or do not liquefy gelatin.

Glucose Gelatin.—This is made by adding to the clear filtered gelatin, prepared as above, two per cent. of glucose. The material is then tubed and sterilized the same as ordinary gelatin. This medium is particularly useful for the cultivation of anaerobic bacteria.

Glucose Litmus Gelatin.—To the glucose gelatin a concentrated solution of litmus is added so as to impart to the medium a deep blue color. This is then tubed and sterilized. During the steaming of this medium the litmus is usually decolorized, but on subsequent cooling the blue color returns. If such a medium is overheated in the process of sterilization the sugar will be altered, and as a result the color of the litmus will change to more or less of a red.

For special purposes other sugars may be added to the gelatin, as in the case of bouillon. A lactose litmus gelatin is very useful in differentiating various organisms. The amount added is usually one or two per cent.

Elsner's Medium.—The addition of gelatin to a potato extract, instead of to a meat infusion, was first resorted to by Holz. Elsner's medium is essentially Holz's potato gelatin, to which one per cent. of potassium iodide is added. It can be used to good advantage in differentiating between the typhoid and colon bacilli, but at the same time it should be remembered that it does not afford an absolute means of detecting the former organism. The method of preparation is as follows: 1,000 gm. of well-cleaned potatoes are cut up

into lumps which are then mashed as fine as possible, best done by passing the material through a fruit press. The finely mashed potatoes are then placed in a meat press and pressure is applied. In this way about 400 c.c. of a dark liquid is obtained from the kilogram of potatoes. The potato juice is then set aside in an ice chest overnight, after which it is filtered through cotton. Ten per cent. of gelatin and one per cent. of potassium iodide are then added to the dark liquid, and the mixture is warmed at about 40° C. until the gelatin melts. Inasmuch as the reaction of this material varies considerably it is necessary now to determine the exact degree of acidity present, and then to reduce this by the addition of the proper amount of alkali, so that the resulting medium has an acidity such that it would require the addition of 20 c.c. of normal alkali per litre to make the solution neutral. The acidity of the gelatin is determined by titrating a portion, say 10 c.c., with decinormal sodium hydrate, using litmus paper as an indicator. If, for example, 10 c.c. require 3.2 c.c. of the decinormal alkali, it will be necessary to reduce the acidity by adding 1.2 c.c. of decinormal alkali, or better 0.12 c.c. of normal alkali for every 10 c.c. of gelatin made. When the proper degree of acidity has been imparted to the medium, the gelatin is placed in a boiling water-bath for three-quarters of an hour until all the proteids have coagulated, after which it is filtered through paper, filled into sterile tubes, and sterilized by steaming for fifteen minutes on each of three consecutive days.

Fish Gelatin.—Five hundred grams of chopped fish are added to 1,000 c.c. of water, and the material is digested the same as given above for ordinary gelatin. To the strained liquid 100 gm. of gelatin, 40 gm. of salt, 5 gm. of glycerin, and 5 gm. of asparagin are added, and the mixture when perfectly fluid is rendered slightly alkaline. It is then heated, tubed, and sterilized as above. This medium is particularly useful for the growth of phosphorescing bacteria.

Nutrient Agar.—One drawback to the ordinary gelatin is that it cannot be used as a solid medium at temperatures above 23° C. This has led to the introduction of agar-agar as a stiffening agent. This substance is a seaweed gathered off the coast of Asia. It has no nutritive qualities of its own nor is it liquefied by bacterial ferments. Therefore it becomes a very useful addition to media for special purposes. The preparation of nutrient agar is very simple. Ordinary bouillon is first made according to the directions already given. The agar may be obtained as a powder or in threads; in the latter case the agar is cut up into very small pieces, and 20 gm. (two per cent.) is then added to the litre of bouillon, which should be in a large flask, or, better, in an enamelled jar. The vessel and contents should then be weighed, after which the liquid should be gently boiled until the agar has completely dissolved. The vessel is now again weighed, and the difference between the two weights is made up by the addition of the proper amount of distilled water.

It is advisable to place the agar now in a water-bath at about 50° C. for several hours in order to allow the sediment to settle as much as possible. The filtration of a two-per-cent. agar is a very slow and tedious process even when carried out in a steam sterilizer. It is sufficient for practically all purposes to filter through a layer of cotton. The filtrate thus obtained is almost, if not entirely, clear; ordinarily whatever little sediment may be present does not interfere with the usefulness of the medium. If much sediment is present in the filtrate, it may be clarified by the addition of egg-albumin as mentioned under the preparation of gelatin.

The filter is prepared by placing a piece of ordinary cotton, about two inches square, in the angle of a large funnel, and then while it is held down by means of a glass rod, a litre or so of very hot water is passed through, once or twice, so as thoroughly to warm the funnel. Eventually the sedimented agar is carefully and slowly decanted on to the cotton filter. If desirable

the agar can be filtered a second time. A very convenient arrangement for the rapid filtration of agar through cotton is shown in Fig. 5064. This consists essentially of a Witte's perforated porcelain plate, which is steadied in place in the funnel by means of a glass rod which passes through the centre. The plate is covered with a layer of cotton on which a similar porcelain plate is placed to prevent the cotton from floating. The funnel is inserted into a strong vacuum flask, which is connected with a Chapman air pump. Boiling water is first passed through the filter to warm it thoroughly, after which the agar is added and suction applied. As soon as the pump begins to act the top plate can be removed.

FIG. 5064.—Filtration Through Cotton Over a Porcelain Plate (Novy).

medium it should be made with only one or one and a half per cent. of agar instead of two per cent., as given above. Such agar is softer and can be passed through a previously moistened filter paper, especially if the funnel is placed in a steam sterilizer or in a funnel-shaped copper water-bath, such as is shown in Figs. 5065 and 5066.

The filtered agar is then tubed and sterilized by steaming one-half hour on each of three consecutive days, after which it is kept in an upright position; or sterilization may be rapidly accomplished by placing the tubes in an autoclave (Fig. 5080) and keeping at a temperature of 120° C. for fifteen minutes. Agar media modified by addition of sugars (or certain chemicals) cannot be sterilized at this high temperature since those constituents are altered. When it is desired to make inclined or slant agar tubes, as many of these as are needed are melted in a water-bath and then inclined so that the agar comes within an inch of the cotton plug.

Thalmann's Agar.—Five hundred grams of meat are boiled for one-quarter of an hour with 1,000 c.c. of distilled water, after which the mass is made up to the original weight and strained through muslin. One per cent. of peptone and 0.5 per cent. of salt are then added and the liquid is boiled, after which it is again made up to the original weight, cooled, and filtered. One and one-half per cent. agar is then added and the weighed liquid is boiled in a concentrated salt-water bath for about three-quarters of an hour, after which it is again made up to the original weight. Thirty cubic centimetres are then titrated with normal sodium hydrate, using phenolphthalein as an indicator. The amount of alkali necessary to neutralize the entire amount of agar is ascertained, and two-thirds of this quantity is then added, in portions and while shaking, to the agar. After heating fifteen minutes the material is filled into tubes.

According to Thalmann and others this medium is adapted for the cultivation of the gonococcus, especially for diagnostic purposes. A little of the pus is mixed with the water of condensation, and then by means of

a wire, rod, or cotton swab the suspension is thoroughly spread over the surface of a series of inclined tubes or over Petri dishes. These when kept for twenty-four hours at 36°–37° show small, glistening colonies, which are single or confluent and appear like highly refractive drops.

The medium is not suitable for subcultures, and Thalmann recommends that the colonies be transplanted to serum bouillon. This is prepared by adding to some bouillon two-thirds to three-fourths of the amount of alkali needed to neutralize the liquid. After heating and filtering, an equal volume of hog serum is added and the mixture tubed. The tubes are inclined and heated for one to two hours at 70° on the first and also on the second day, and for one hour at 100° on the third day. According to Wassermann hog serum is just as good as human serum for cultivating the gonococcus.

Glucose Agar.—This is made by adding to the filtered agar, or to so much of it as may be wanted, two per cent. of glucose. The medium is then tubed and sterilized in the ordinary way. It is used especially for the growth of yeasts and anaerobic bacteria. If desired, it may be colored with litmus as in the case of gelatin. Lactose, maltose, saccharose, or other sugars may be used as a modification, instead of glucose. The medium in either case is made in the same manner, with similar percentages of sugar.

Rothberger's Neutral-red Agar.—This can be made by adding to a 0.3-per-cent. glucose agar one per cent. of a saturated aqueous neutral red solution. The typhoid bacillus does not change the color or produce gas, whereas the colon discharges the red and leaves a fluorescing color. The inoculation can be made either by planting a shake culture or by making a stab culture, which can then be covered with a layer of agar to exclude air changes. The addition of neutral red to bouillon is of service in water examinations (Irons, Jordan).

Endo's Fuchsin Agar.—When properly prepared, this medium ranks among the first as a reliable means of differentiating the *Bacillus typhosus*. It is prepared as follows: To 1,000 c.c. neutral three-per-cent. agar (made in the regular way) add 10 gm. chemically pure milk sugar (lactose); 5 c.c. alcoholic solution of fuchsin (freshly filtered); 25 c.c. ten-per-cent. solution sodium sulphite; 10 c.c. ten-per-cent. solution of soda. The milk-sugar solution and fuchsin solution are added first to the dissolved agar and well mixed. The solution of sodium sulphite is added gradually until the color of the medium disappears. On solidifying, the medium should remain colorless. Put in tubes (about 15 c.c. each) and sterilize in steamer for thirty minutes on three consecutive days. Keep tubes in the dark until ready for use.

Endo ascribes the resulting color changes to the fact that fuchsin is a hydrochloric-acid combination of rosanilin. Rosanilin is a colorless leucobase, but, in combination with acids, gives colored compounds. The sodium sulphite used in the medium is just sufficient to reduce to the colorless base, thus giving a practically clear medium.

In the presence of sugar of milk such organisms as *B. coli* liberate lactic acid, which in turn acts upon the leucobase, and gives a deep red combination. But the colonies of *B. typhosus* developing in this medium do not produce an acid, therefore they have a clear glassy appearance, or slightly bluish in transmitted light.

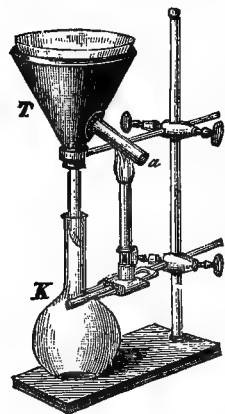


FIG. 5065.—Double-Walled Hot-Water Funnel.



FIG. 5066.—Single-Wall Hot-Water Funnel with Ring Burner.

Plates are made and inoculated in the ordinary manner from infective material. Incubation is carried out at 37° C. and, when suspected colonies develop, they may be fished out, transplanted, and given the agglutination test with specific serum to identify positively.

The Malachite-green Enriching Method of Lentz.—This method has also been used extensively in the separation of the typhoid bacillus, especially in the cultivation from fæces. The use of malachite green for this purpose was first introduced by Loeffler. Lentz and Tietz have modified and improved the method. They direct that three pounds of chopped lean beef be macerated in two litres of water for sixteen hours. Express the extract, cook for one-half hour and filter, add three per cent. agar to the filtrate and cook slowly for three hours to dissolve. Then add one per cent. peptone; 0.5 per cent. sodium chloride; and one per cent. nutrose (may be omitted). Make neutral to litmus with soda solution, boil, and filter into small flasks of 100 c.c. to 200 c.c. capacity. Before adding the malachite-green solution, test with neutral litmus paper, and slowly alkalize with sterile soda solution until the litmus strips give a distinct red violet. The crystals of malachite-green (Hoechst) should be used to make this solution. Lentz used different concentrations of the dye in preparation of the medium, but Simon recommends a concentration of 1:22,000 as being the most favorable. In such case make a fresh solution of 1:220, and of this add 1 c.c. to each 100 c.c. of the hot agar, thus obtaining the required concentration. The medium is poured in Petri dishes, and allowed to cool for use. Inoculations may be made upon its surface. The dye inhibits the growth of *B. coli* and many other organisms but in the above concentration the *B. typhosus* develops slowly, usually from two to four days. When kept in the incubator at 37° C. typhoid colonies give the agar a yellow color. Test by specific agglutinating serum to identify. Results obtained by different observers have varied. It seems to be difficult to secure a uniform preparation of malachite green.

Lactose Litmus Agar.—This medium was introduced by Wurtz, and is very useful in differentiating between the typhoid and colon bacilli. Acid formation in the case of the latter is indicated by a change in the reaction of the litmus. If this medium is made by the addition of two per cent. of lactose and litmus to the ordinary agar it will be found that even typhoid bacilli will give a slight acid reaction. This, however, is not due to the fermentation of the lactose, but to the small amounts of muscle sugar derived from the meat. It is therefore desirable that the agar for this purpose should be made out of sugar-free bouillon, which can be prepared according to the directions already given. Prolonged boiling of the agar must be avoided, inasmuch as the agar itself, since it is a complex carbohydrate, may split off some sugar.

It is often preferable to make the plain lactose agar and to add to the tubed and sterilized medium, whenever needed, by means of a sterile pipette, a sterile litmus solution. Obviously other indicators, such as rosolic acid, neutral red, etc., may be added in the same way.

Glycerin Agar.—To the ordinary nutrient agar prepared as above, five per cent. of glycerin is added. The addition of glycerin serves to keep the surface of the medium moist, and at the same time imparts nutri-

ties to acid production when grown on mannite media, whereas the typhoid bacillus does. The agar should be prepared from sugar-free bouillon, and to it one or two per cent. of mannite is then added. Litmus may be added to the bulk medium before it is tubed, or the sterile litmus solution may be added to the sterile tubed agar by means of a pipette whenever needed.

Pfeiffer's Blood Agar.—This is made by spreading over the surface of ordinary inclined agar a few drops of human blood. On the surface thus prepared one is able to cultivate the influenza bacillus. The blood from the lower animals can be used in like manner to good advantage.

The human blood required for this and similar purposes can be drawn without difficulty by means of a sterile syringe from the large median vein just below the flexure of the elbow. The superficial circulation should first be impeded by means of a rubber tube tied about the middle of the arm. The surface of the skin over the vein to be punctured is thoroughly cleaned by means of a disinfecting solution, such as mercuric chloride or lysol. The needle of the sterile syringe is then introduced into the vein, and as the piston is slowly withdrawn the syringe fills with blood. Five or ten cubic centimetres of blood can thus be obtained in a few minutes. When the needle is withdrawn a compress of cotton, soaked in mercuric chloride, should be applied to the wound. The blood must be at once transferred to either the surface of inclined agar or to previously melted agar, cooled to 50° C. In the latter case it is mixed at once, and the tube is then set aside in an inclined position to solidify.

Blood-agar Mixture.—As just described, human blood may be mixed with melted agar, cooled to 50° C., after which the mixture may be allowed to solidify in an inclined position. For diagnostic purposes this procedure has been utilized to detect the presence in the blood of typhoid bacilli, gonococci, and other organisms. Instead, however, of allowing the blood mixture to solidify in the tube it is poured out into a sterile Petri dish, and in this way a blood-agar plate is obtained, on which eventually colonies of the suspected organism may develop. The presence of a very few organisms can thus be detected in 1 or 2 c.c. of blood, which would not be possible by direct examination or by staining. The amount of blood which is added to the agar may be varied according to circumstances. Thus it may be one to four, one to two, or even one to one.

Blood from the lower animals can be drawn under strictly aseptic conditions into sterile Nuttall's blood pipettes, or into the modified form of Novy, shown in Fig. 5067. This can be easily made from test tubes of various sizes, according to the kind of animal to be bled. Thus a five-eighths by five-inch test tube may be used for bleeding a mouse or rat, while a one- by eight-inch tube would be used in the case of a rabbit. The bottom of the test tube and the end of a piece of glass tubing are softened in the flame of a blast lamp and then brought together. A narrow blas flame is then directed against the test tube about an inch from the bottom. On slow rotation in a horizontal position a thickened constriction results, and as soon as this is sufficiently thick the two ends are drawn apart slowly. A tapering capillary results, which is then sealed in the flame at a point about two inches from the tube proper. The tube is then plugged with cotton and sterilized by dry heat. When it is desired to prepare sterile defibrinated blood a drawn-out tube or a narrow glass rod is passed through the centre of the plug. By moving this about, after the blood has been received in the pipette, complete defibrination can be obtained, and that without any contamination from the outside.

In the case of the larger animals the blood is best drawn from the carotid artery. For this purpose the animal is anaesthetized and the artery exposed for about an inch. After the first incision it is advisable to avoid the use of cutting instruments, and instead to separate the tissues with the fingers. Pressure forceps is then

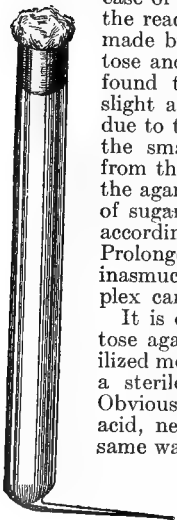


FIG. 5067.—Blood Pipette, Novy Form.

tive qualities to the agar. This medium is very valuable for the growth of diphtheria, glanders, pneumonia, and tubercle bacilli.

Mannite Agar.—Mannite, which like glycerin is a polyatomic alcohol, was first used by Norris and Hiss as a means of differentiating the typhoid from the dysentery bacillus. The latter organism does not give rise

applied at the distal end of the artery. Another pair is then applied about an inch below this point. A finger is then placed under the clamped portion of the artery and a very slight opening is made into the blood-vessel. The blades of a very narrow-pointed pair of forceps are then introduced into the opening, and, when distended, the tip of the sterile blood pipette can readily be introduced. Before this is done, however, the tip should be scratched with a file, then broken off, and the open end should be flamed for a moment to insure sterility and to round off the sharp edge. As soon as the pipette is in position the lower clamp is removed, when the blood rapidly rises in the tube. If defibrinated blood is desired, the blood should be stirred by an assistant. When serum is wanted, this stirring is omitted. As soon as blood ceases to flow, the pipette is removed and the tip is sealed in the blast lamp.

Obviously in the case of small animals, such as the mouse or rat, this procedure is not applicable. The blood may be drawn up into a syringe from the artery. A much better way, however, which has been used for several years in the author's laboratory, is to take the blood directly from the heart into a small pipette of the same form as that used for the larger animals. For this purpose the thorax is opened, the heart is freed from the pericardium and raised by means of oval-tipped forceps. The end of the pipette is then introduced into the right ventricle. Suction may be applied to the end of the pipette in order to obtain the fullest possible yield.

Blood can be drawn from very large animals, such as the horse, by introducing a trocar into the jugular vein. This is the procedure which is followed in the preparation of antitoxins. The trocar is connected by means of a short rubber tube with a glass tube, which is inserted into the receiving cylinder. In this way several litres of blood can be drawn from the horse at each bleeding.

In ordinary laboratory work the blood which has been collected in the glass pipettes is then transferred to melted agar, which has been previously cooled in the water-bath to 50° C. The amount of blood which is added to each tube will vary with the purpose in view. It may be one part of defibrinated blood to ten of agar, or one to five, one to two, or one to one, as the case may be. Exceptionally mixtures of two to one and three to one are used. The blood is then mixed with the agar and the tubes are set aside to solidify in an inclined position. The transfer of the blood to the tubes is best accomplished by means of a sterile drawn-out bulb pipette, such as is shown in Fig. 5096, c.

The blood agar thus prepared requires no further sterilization, for if the operation has been properly carried out no organisms will be present. The tubes can be used for culture purposes at once, or they may be kept for several days to allow any organisms which might be present to develop. This blood medium is invaluable for the cultivation of various pathogenic organisms. On such media it has been possible, for example, to grow for the first time pathogenic protozoa—*Trypanosoma lewisi* of rats and *Trypanosoma brucei*, the cause of nagana or the tsetse-fly disease (Novy and McNeal).

Novy and McNeal's Blood Agar for Trypanosomes.—Novy and McNeal have succeeded in cultivating a number of the *Trypanosomata* (*Tr. lewisi*, *Tr. brucei*, *Tr. evansi*, and others) upon a specially prepared artificial medium. It is made as follows: 125 gm. of rabbit or beef meat is extracted in 1,000 c.c. of distilled water; add two per cent. of Witte's peptone, one-half per cent. of salt; and two per cent. of agar. Then make alkaline by adding 10 c.c. of normal sodium carbonate. The agar thus prepared is tubed and sterilized in an autoclave at 110° C. for thirty minutes.

When cooled to about 50° C., two volumes of defibrinated rabbit's blood are added and the mixture is allowed to solidify in an inclined position. After the agar has solidified, the water of condensation which settles at the bottom of the tube is inoculated with a

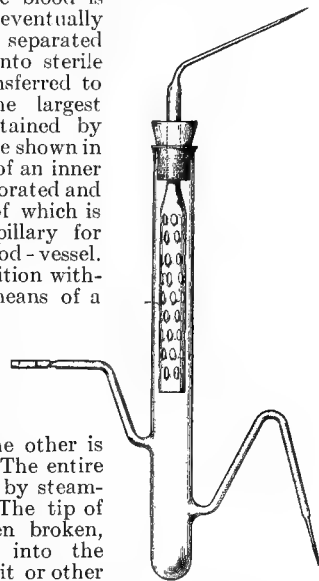
drop of freshly drawn blood from the infected animal. The above investigators found that even the first generation thrives upon this medium and transfers grow luxuriantly.

Serum Agar.—This is made by adding variable amounts of sterile serum to the melted agar, which has been cooled to 50° C. in the water-bath. The serum can be obtained by collecting the blood, as given above, in sterile pipettes. The blood is allowed to clot, and eventually when the serum has separated it can be drawn up into sterile bulb pipettes and transferred to the melted agar. The largest yield of serum is obtained by using the Latapie pipette shown in Fig. 5068. This consists of an inner tube, which is freely perforated and the narrow, outer end of which is drawn out into a capillary for insertion into the blood-vessel. This tube is held in position within the outer one by means of a rubber stopper. The outer receiving tube, which is about an inch in diameter, is provided with two side tubes, one of which is drawn out and sealed while the other is plugged with cotton. The entire pipette is first sterilized by steaming in an autoclave. The tip of the inner tube is then broken, flamed, and inserted into the carotid artery of a rabbit or other animal. The blood should not fill the pipette beyond the inner tube. The tip is then sealed and the pipette is allowed to remain in a vertical position until the blood has firmly clotted. It is then inverted and the serum, as it is squeezed out of the clot, falls to the bottom. The purpose of the perforated inner tube is to allow more complete shrinking of the clot. The serum drains away at once from the clot, and is therefore perfectly clear. When it is desired to remove the serum the tip of the side tube is scratched with a file, then broken off, and the end is flamed to insure absence of bacteria. The tube is then inserted into a sterile test tube or flask and by blowing into the other side tube the serum is forced out. It can then be distributed to the agar tubes by means of a sterile bulb pipette. These are then allowed to solidify in an inclined position. As in the case of blood agar the medium prepared in this way is perfectly sterile, if the manipulation is properly carried out. Inasmuch as sterilization by heat is avoided, the proteid constituents of the serum remain in as near to the native condition as possible. Such serum agar makes an excellent medium for the pneumococcus and for other organisms. Obviously, serum-agar plates can be prepared, if it is so desired, in which case the melted and cooled agar is inoculated with the organism to be cultivated, after which the serum is added and mixed with the agar, which is then poured out into sterile Petri dishes.

FIG. 5068.—Blood Pipette of Latapie.

Serum agar, made by adding human blood serum to melted agar, has been used for the cultivation of the gonococcus (Wertheimer). Ascitic or pleuritic fluid may also be added to agar in the proportion of one part of the fluid to two parts of the agar. Such agar is used especially for the cultivation of the gonococcus. The ascitic, pleuritic, or hydrocele fluids may be sterilized by fractional sterilization or by filtration through a Berkefeld filter under pressure.

Wassermann's Serum-nutrose Agar.—This also has been found useful for cultivating the gonococcus. Five cubic centimetres of hog serum is added to 30 to 35



c.c. of water, 2-3 c.c. of glycerin, and 0.8-0.9 gm. of nutrose. Nutrose is a sodium-phosphate casein compound, and when added to serum prevents coagulation on boiling. The solution is boiled for twenty minutes, after which it is added in equal parts to two per cent. peptone agar in test tubes. This mixture is then poured into Petri dishes. Nutrose has been used also in the preparation of the Drigalski-Conradi agar. Hog serum, which is said to be as good as human serum for cultivating the gonococcus, has been employed also by Thalmann.

Drigalski-Conradi Agar.—This is a meat-peptone-nutrose agar containing lactose, litmus, and crystal violet. The preparation is as follows: 1. A mixture of three pounds of meat and two litres of water is allowed to stand for twenty-four hours; the expressed meat juice is then boiled for one hour and filtered. To the filtrate are added 20 gm. of Witte's peptone, 20 gm. of nutrose, 10 gm. of sodium chloride, and the whole is boiled for one hour and filtered. To this filtrate 60 gm. of agar is added and the liquid is boiled for three hours, or one hour in an autoclave. It is then rendered alkaline to litmus paper, boiled half an hour, and filtered. 2. A solution of litmus is prepared according to Kubel-Tiemann as follows: The powdered commercial litmus is repeatedly extracted with hot distilled water. The liquid is acidulated with dilute acetic acid and evaporated to syrupy consistence on a water-bath. The thick fluid is then diluted by the gradual addition of ninety-per-cent. alcohol, transferred to a flask, and an excess of ninety-per-cent. alcohol is added. This precipitates the blue pigment, while the red dye and the potassium acetate remain in solution. The precipitate is filtered and washed with alcohol, then dissolved in distilled water, after which the solution is warmed and filtered. The filtrate is then added gradually to very dilute sulphuric acid (one or two drops of acid to 200 c.c. of water) till the color changes to a wine red. The concentrated blue is then added till the blue color is restored; 260 c.c. of this litmus solution is boiled for ten minutes, then 30 gm. of pure lactose is added, and the boiling is continued for fifteen minutes. 3. The hot litmus is added to the hot agar, mixed, and the reaction is made slightly alkaline; 4 c.c. of a hot sterile solution of ten-per-cent. anhydrous soda and 20 c.c. of a freshly prepared solution of 0.1 gm. of crystal violet in 100 c.c. of warm sterile water are then added, after which the material is filled into tubes or flasks. Excessive heating should be avoided, inasmuch as it alters the lactose. The crystal violet is intended to restrict the development of the unimportant bacteria.

The Drigalski-Conradi medium has been recommended for the isolation of the typhoid bacillus. For this purpose the faeces should be diluted with ten to twenty volumes of salt solution. The authors employ large plates, 15-20 cm. in diameter. The agar is poured into the dishes to a depth of at least 2 mm., and the cover is then kept off till the moisture has dried from the surface of the agar. By means of a 5-mm. glass rod, bent at right angles and previously dipped in the suspension, a series of streaks are made over a number of the dishes. The inoculated plates are then kept at 37° C. for twenty-four hours. The colon colonies are large, opaque, and red, while the typhoid are small, glassy, and resemble dewdrops. The further identification of the suspected colony is made by applying the agglutination test and by growing in Rothberger's neutral red agar.

MacConkey's Bile-salt Agar.—This medium is prepared by dissolving one and one-half or two per cent. of agar in bile-salt bouillon stock solution (see above). If necessary clear with egg-albumin. Neutral red and a given sugar are then added, as in the case of the broth preparation. It is used in the examination of faeces, sewerage, etc., for intestinal bacteria. The method of procedure is practically the same as that given under the Drigalski and Conradi medium. The growth of most bacteria is inhibited, while that of *B. coli* and *B. typhosus* is not. Colonies of acid-producing bacteria

appear rose-red in color. Alkali gives a yellow-red with this indicator on plates. Other modifications are used by water analysts.

Matzschita's Liver-gall Agar.—This medium is especially recommended for the cultivation of the intestinal flora. It is prepared as follows: Take 500 gm. of finely chopped ox-liver; 30 gm. peameal; add one litre of distilled water and cook until the soluble constituents are extracted. The residue is removed by straining through muslin, and to the filtrate add 7 gm. peptone, 5 gm. sodium chloride, and 0.2 gm. hydrochloric acid. The whole is carefully shaken and then allowed to stand at 37° C. for three hours. After this 600 gm. of ox-gall is added, and the whole is again allowed to stand for three hours at incubator temperature. It is then heated for some time, filtered, and sufficient agar (two per cent.) is added to give solid medium. Filter, place in tubes, and sterilize. This medium, notwithstanding the addition of the hydrochloric acid, remains slightly alkaline. Matzschita recommends, for the culture of intestinal bacteria, that the medium be neutral or very slightly acid.

Gelatin Agar.—Several formulas have been proposed for the preparation of this medium. Each finds its special application. That of Capaldi was recommended for the isolation of the typhoid bacillus from faeces. It is made by dissolving 20 gm. of Witte's peptone, 10 gm. of gelatin, 10 gm. of glucose or of mannite, 5 gm. of sodium chloride, and 5 gm. of potassium chloride in 1,000 c.c. of water. The solution is filtered and two per cent. of agar is added and dissolved by boiling, after which it is rendered alkaline by the addition of 10 c.c. of normal alkali. The filtered solution is then tubed and sterilized by steaming.

Beer-wort Agar.—Wort is of particular value in the cultivation of yeasts and it is also used in the study of certain bacteria. It may be used in the fluid form, or solidified by means of either gelatin or agar. Eyre recommends its preparation by taking 250 gm. of crushed malt and placing it in a two-litre flask with 1,000 c.c. distilled water. The mixture is first heated up to 70° C. in the stoppered flask, then placed in a constant-temperature water-bath, and allowed to macerate at 60° C. for one hour. The fluid portion is separated by straining through muslin; then it is heated for thirty minutes in a steam sterilizer and followed by filtration. The natural reaction of the resulting wort is left unchanged.

In case the solid preparation is desired, add two per cent. agar and proceed the same as in the preparation of nutrient agar. Sterilization is carried out by placing in a steam sterilizer at 100° C. for twenty minutes on each of three consecutive days.

Stoddart's medium is a gelatin agar which contains five per cent. of gelatin, one per cent. of peptone, and a half per cent. each of agar and of salt. A litre of meat extract is prepared in the usual way. In this 10 gm. of peptone and 5 gm. of salt are dissolved, and the solution is then divided into two parts. To one portion ten per cent. of gelatin is added, and when this has dissolved, the solution is neutralized and an excess of 10 c.c. of normal alkali per litre is added. The other half of the meat extract is likewise neutralized, and then 10 c.c. of the normal alkali is added per litre to impart the requisite reaction. The liquid is then measured or weighed, boiled, and filtered. Five grams of cut agar is added to the bouillon, which is then boiled until the agar dissolves. Distilled water is added to make up to the original volume or weight, after which the two liquids are combined and allowed to sediment. The entire product is finally filtered through cotton or, better, through paper. The medium is filled into tubes which are then steamed for fifteen minutes on each of three consecutive days. To use this medium, it is poured out into sterile Petri dishes, and when solidified the centre is touched with the organism to be tested. The typhoid bacillus, on account of its motility, spreads rapidly over the surface as an almost transparent growth whereas that of the colon bacillus spreads less and is easily visible.

Guarnieri's gelatin agar is made in a somewhat similar manner. Three grams of powdered agar is emulsified with 50 c.c. of distilled water, and this is then added to a solution of 50 gm. of gelatin in 750 c.c. of meat extract. The whole is boiled till the agar has dissolved, when a solution of 25 gm. of Witte's peptone and 5 gm. of salt is added. The entire liquid, which now makes up to one litre, is then carefully neutralized with normal alkali, using litmus as an indicator. The medium is tubed and sterilized as usual. It has been used to advantage in the cultivation of the pneumococcus.

Weil's Meat-potato Agar.—The potato juice is prepared as in the method of Holz or Elsner; 300 c.c. of this is added to 200 c.c. of slightly alkaline bouillon; 3.75 gm. of agar is then dissolved in the liquid, thus yielding a 0.75-per-cent. agar solution. The typhoid bacillus presents threaded colonies on this medium, the same as in Elsner, Hiss, and Piorkowski media.

Substitutes for the Meat Infusion.—In the preparation of the foregoing media a meat infusion serves as the basis in each case. In special instances, but not as routine procedure, these media may be modified by using the commercial Liebig's beef extract in place of the meat infusion. The chief advantage lies in the fact that the beef extract can be kept always on hand. At the same time it must be remembered that media made up with such extract are by no means as nutritious as those made up with the meat infusion. The amount of Liebig's extract which is used varies with different workers. In general, from 1 to 3 gm. is added to one litre of water; 5 and even 10 gm. may be used. To this solution peptone and salt may be added in the usual amounts. The liquid when rendered alkaline and filtered constitutes a Liebig's-extract bouillon. In the same way gelatin and agar media are prepared.

Peptone Substitutes.—Several compounds have been suggested as substitutes for Witte's peptone. In Martin's and Peckham's bouillon and in Deycke's agar this peptone is replaced by that which is formed by the digestion of the muscle tissue. In other media derivatives of albumen or casein are employed. Heyden's "Nahrstoff" is a digested egg albuminate, while nutrose is a casein compound. The addition of lecithin, protogen, and hæmoglobin, etc., is made with the object of improving the nutritive qualities of the media.

Hiss' Tube Medium.—This is used as a means of testing for the typhoid bacillus. It is made by adding 5 gm. of Liebig's extract, 5 gm. of salt, and 5 gm. of agar to 1,000 c.c. of water. The mixture is then heated until the agar has dissolved, after which the water which is lost by evaporation is replaced and then eight per cent. gelatin is added. As soon as the gelatin has dissolved, the liquid is partially neutralized by the addition of normal alkali. The reaction is left acid, and to such an extent that it would require 15 c.c. of normal alkali per litre to make the solution neutral to phenolphthalein. The liquid is then cooled to 60° C. and cleared by the addition of the white of an egg stirred up in about 25 c.c. of water. The liquid is then boiled for a few minutes, after which 10 gm. of glucose is added. After sedimentation at 50° C. the medium can be filtered through paper or cotton and tubed. This medium is used only for stab cultures. Diffusion of the growth through the medium in the case of very motile organisms, such as the typhoid bacillus and the production or absence of gas, are the criteria sought for.

Hiss' Plate Medium.—Hiss utilized the tendency of the typhoid bacillus to form threaded colonies when grown on soft media, as a means of differentiation from the colon bacillus. The medium, as first proposed, contained 15 gm. of agar, 15 gm. of gelatin, 5 gm. each of Liebig's extract and of sodium chloride, 10 gm. of dextrose, and 1,000 c.c. of distilled water. This was cleared by the addition of the whites of two eggs and filtered through absorbent cotton. The reaction was left acid, and of such extent that it would require the addition of 2 c.c. of normal alkali to make it neutral to phenolphthalein. Subsequently Hiss made various modifications of

this formula, eliminating the unnecessary constituents. The simplest combination, which was found to give excellent results, was made by adding 15 gm. of agar and 5 gm. of Liebig's extract to 1,000 c.c. of distilled water. No acid or alkali was added. The medium was cleared by the whites of two eggs and filtered through cotton. Plate cultures, made at 37° C., show excellent differentiation between the colonies of typhoid and colon bacilli in twenty-four hours. The former show threaded colonies, the latter do not.

Hesse's Nahrstoff-Heyden Agar.—The "Nahrstoff-Heyden" is an albumose made from egg-albumin. It should first be stirred up in a beaker with a little water, and then added to the liquid. For cultivating the tubercle bacillus the medium consists of: 5 gm. Nahrstoff-Heyden, 5 gm. salt, 30 gm. glycerin, 10 gm. agar, and 1,000 c.c. of distilled water; 5 c.c. of normal soda solution is added. The latter represents a 14.3 per cent. of the crystalline salt ($\text{Na}_2\text{CO}_3 + 10 \text{H}_2\text{O}$) and not 28.6 per cent., as stated by Hesse. The Hesse-Niedner agar, which has been recommended for the study of water bacteria, is made by dissolving 7.5 gm. of Nahrstoff-Heyden and 12.5 gm. of agar in 1,000 c.c. of distilled water. Gage and Phelps dissolve one per cent. each of agar and of the Nahrstoff in 1,000 c.c. of distilled water, and make the solution neutral to phenolphthalein.

Blood Serum.—The preparation of serum from small animals has been described at length under serum agar. When it is desirable to use large quantities of serum it is advisable to collect ox blood at a slaughter-house. The more care taken in collecting the blood under aseptic conditions the less troublesome will be the subsequent sterilization. A convenient receptacle is a half-gallon battery jar covered with paper and previously sterilized. The spurting blood is received directly into the jar, after which the paper cap is replaced and the blood set aside until it firmly clots. It can then be transported to the laboratory and set aside in a cool place for the serum to separate. The serum can then be drawn up by means of an aspirator into a sterile globe receiver, such as is shown as a part of Fig. 5072. It can then be conveniently filled into test tubes or into flasks.

The earliest method of sterilizing blood serum is that of Koch by fractional heating. The tubes are placed in an inclined position in a serum coagulator shown in Fig. 5069. The Roux water-bath, shown in Fig. 5075,

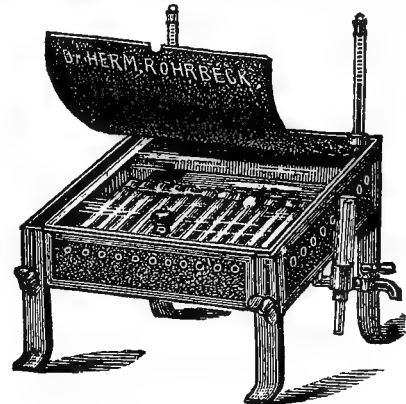


FIG. 5069.—Koch's Blood-Serum Coagulator.

is particularly useful for this purpose. The serum tubes are immersed in the water at 58° C. and are heated for an hour at 58° C. on each of seven successive days. This low temperature is selected in order to accomplish the sterilization and yet keep the serum in a fluid condition. Unfortunately bacteria may be present in the serum which will actually grow at the temperature employed, and in that case this method of sterilization is inapplicable. Some have endeavored to obviate this difficulty by filtering the serum through a Berkefeld

bougie. Martin suggested that one to two per cent. of chloroform be added to the serum, which is then set aside for several months, after which the chloroform can be driven off by heating at 65°. Fraenkel dispensed with the sterilization, relying entirely upon the aseptic collection of the serum. When the serum is collected with the care outlined above, it will be found that very few bacteria are present. Consequently after the tubes have been filled with the serum they may be incubated for several days, and at the end of that time the contaminated ones can be discarded. This procedure is preferable to those just given. The sterile serum is then coagulated in an inclined position by raising the temperature of the sterilizer to 65° C., and keeping it there until the serum has become solid. The medium thus prepared is transparent and solid. When a higher temperature is used, the serum coagulates to an opaque white mass.

Inasmuch as the above methods require much time and skill and are in themselves very tedious, they have been largely supplanted by fractional sterilization in steam. For this purpose the tubes are first placed in an inclined position, either in a dry-heat oven, or, better, in the coagulator, and then heated to 85° to 95° C. until firm coagulation results. If this is not looked after, the medium will be torn up by gas bubbles during the next step. The coagulated-serum tubes are then placed in wire baskets and steamed, as in the case of agar, for half an hour on each of three consecutive days. The medium thus prepared is fully as useful as that which is transparent.

Löffler's Blood Serum.—This consists of one part of a one-per-cent. glucose bouillon and of three parts of blood serum. This mixture is filled into tubes and sterilized in the manner just given. It is used very extensively for the diagnosis of diphtheria.

Alkaline Blood Serum (Lorrain Smith).—To each 100 c.c. of blood serum add 1.0–1.5 c.c. of a ten-per-cent. solution of sodium hydrate, and shake gently. Place in tubes and sterilize as mentioned under blood serum. A clear solid medium results, consisting principally of an alkali-albumin. This medium is also used in the cultivation of *B. diphtheria*.

Glycerin Serum.—Five per cent. or more of glycerin is added as in the case of glycerin agar. The sterilization is the same as that just given. It is used for the cultivation of the tubercle bacillus.

Serum-water Media.—When serum is diluted with five to ten parts of water it can be sterilized by steaming without coagulation taking place. Hiss employed such a medium in differentiating between the pneumococcus and streptococcus; also in distinguishing between the dysentery and allied organisms. He prepares the medium by adding one part of clear beef serum to two parts of distilled water. The mixture is first heated to 100° for a short time, so as to destroy the glycolytic enzyme which is present, after which one per cent. of the sugar desired is added. Dextrose, galactose, mannite, maltose, lactose, saccharose, inulin, and dextrin have been thus used. The medium is colored by the addition of one per cent. of a five-per-cent. aqueous litmus solution. The medium is then tubed and steamed for ten minutes on three consecutive days.

Marmorek's Media.—In order to maintain streptococci at their maximum virulence Marmorek used several media, preference being given to them in the following order:

1. Human serum 2 parts, bouillon 1 part.
2. Pleuritic or ascitic fluid 1 part, bouillon 2 parts.
3. Serum of mule or ass 2 parts, bouillon 1 part.
4. Horse serum 2 parts, bouillon 1 part.

These media can be sterilized by fractional heating at low temperature, or, better, by filtration through a Berkefeld bougie.

Thalmann's serum bouillon for cultivating the gonococcus has been mentioned in connection with his agar.

Milk.—This is an excellent medium for diagnostic purposes. It is advisable to use centrifugated milk if

possible. Otherwise the whole milk is placed in a beaker or flask and steamed for about half an hour. When partially cooled it can be poured into a large separatory funnel, or into a bulb receiver shown as part of Fig. 5072, and allowed to stand thus overnight. The underlying layer of fat-free milk can then be filled directly into tubes. These are then sterilized by steaming half an hour on each of three consecutive days. When time is an object the whole milk may be filled directly into tubes. If desired the milk may be colored with litmus. Instead of milk, whey may be used to good advantage. This can be prepared by coagulating the milk with rennet. The liquid is first separated by means of cheesecloth and finally put through paper. It is then colored with litmus, filled into tubes, and sterilized. Care must be taken not to overheat the milk lest the lactose undergo more or less oxidation. Whey-gelatin and whey-agar are used for special purposes.

Petruschky's Litmus Whey.—Very dilute hydrochloric acid is added to slightly warmed, fresh milk. The casein is precipitated and removed by filtration. The acid is just neutralized by the addition of dilute sodium hydrate solution, then the fluid is steamed for two or three hours, thus throwing out any acid albumin which might have been in the solution. The fluid when filtered off through paper should be just neutral and colorless. Litmus solution is added in sufficient quantity to give a distinct tint. Sterilize as in ordinary milk tubes.

Urine.—By discarding the first portion of urine which is passed, the remainder can be collected in sterile flasks and will be free from bacteria. Such urine may be used directly for studying the various fermentations which it may undergo. To prepare a urine gelatin the secretion should be diluted so as to have a specific gravity not to exceed 1.010. Ten per cent. of gelatin is then added, and when it has dissolved the reaction is made to correspond to that of the original urine. Heller's urine gelatin is prepared in the same way, but has one per cent. peptone and a half per cent. of salt. After solution the liquid is rendered faintly alkaline, then filtered and tubed.

Piorkowski Urine Gelatin.—Normal urine of 1.020 specific gravity is collected for two days, and is allowed to become slightly alkaline in reaction. Then 1.5 per cent. peptone and 3.3 per cent. gelatin are added, and the mixture is heated for one hour on the water-bath, after which it is filtered and filled into tubes. These are sterilized by heating at 100° for fifteen minutes on the first day, and for ten minutes on the second day. The medium is used to differentiate the typhoid from the colon bacillus. Petri plates are made and developed at 22° C. for twenty-four hours. While the colon colonies are roundish, finely granular, sharp-bordered, and yellowish, the typhoid colonies are small and show a more or less marked threaded border. This method has given good results in connection with the examination of typhoid faeces.

Urine Agar.—This can be prepared by adding to the freshly passed urine two per cent. of finely cut agar. The mixture is then boiled until solution results, when it is filtered through cotton or paper as in the case of ordinary agar. This agar is then filled into tubes and sterilized by steaming.

Another way of preparing a urine agar is to collect the urine, after discarding the first portion which is passed, in a sterile flask, and then to transfer it by means of a pipette, as in the case of blood or serum, to the melted and cooled agar. One part of urine to two parts of agar is ordinarily used. Normal or albuminous urine may be used for this purpose, and with very little care the urine can be collected entirely free from bacteria. Such urine agar has been used to advantage for growing the gonococcus.

Ox-bile Medium.—Conradi, Coleman, and Buxton, as well as others, have recommended ox-bile media in making direct cultural examinations of blood from typhoid-fever patients. Ox bile possesses certain advantages for this particular work since it prevents coagulation of

blood, inhibits the bactericidal action of freshly drawn blood, and at the same time serves as an excellent culture medium for *B. typhosus*. Coleman and Buxton prepare their medium by adding 2 gm. peptone and 10 c.c. glycerin to 90 c.c. ox bile. The mixture is placed in flasks of 20 c.c. each and sterilized. The blood (3 c.c.) from the patient is placed in flask, then incubated. The organisms develop rapidly, usually in from twelve to fourteen hours. Transplants are made to other media for further growth and diagnosis.

Internal Organs.—For special use the several media, such as bouillon, agar, and gelatin, may be made up with the finely divided organs in place of the minced meat. At times the solid organs are sterilized and used as such. For this purpose the spleen, liver, pancreas, brain, intestinal mucosa, etc., have been used. Matzushita recommends their use in agar preparations (as a substitute for the ordinary beef) for the special study of the flora of the intestinal canal. The steamed brain, for example, when cut up into slices and sterilized, can be used for cultivating the tubercle bacillus (Ficker) and also the gonococcus (Thalmann).

Egg Media.—Hueppe first suggested the use of fresh eggs as a culture medium. For this purpose the shell is thoroughly cleaned and disinfected with mercuric chloride. A small opening is then punched through the shell, and through this the organism to be tested is introduced into the inside. The opening is then sealed with a bit of sterile paper and collodion. Another procedure is to insert through the opening in the shell a rather wide, drawn-out tube pipette. On applying suction, especially with the aid of an aspirator, the contents of the egg can be drawn up into the bulb, and can then be distributed to tubes (Novy).

The egg may be used as a solid opaque medium according to Wesener. The egg is thoroughly agitated so as to mix the yolk with the albumen. It is then coagulated at 75° to 80° C., after which the shell is removed

and the egg is cut up into slices and placed in suitable dishes and sterilized by steam. In like manner the coagulated white of the egg may be cut up into slices and tubed. A transparent, coagulated egg albumin may be prepared by converting it into an alkali albuminate, as suggested by Tarchanow and by Karlinski. For this purpose the egg is placed in ten-per-cent. potash for fourteen days, after which the shell is removed and the solidified egg is cut up into slices, tubed, and sterilized.

Potatoes.—These may be prepared in several ways. The old method, introduced by Koch, is still used where mass cultures are desired. The potatoes are scrubbed clean under the tap, and any bad spots carefully removed by means of a knife.

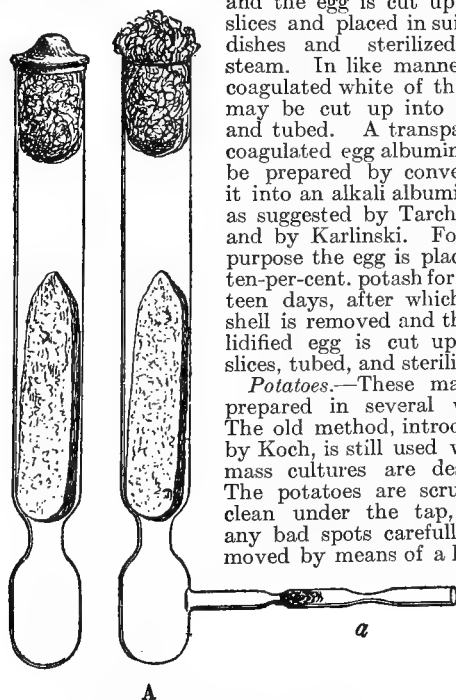


FIG. 5070.—Roux Tube for Potato Culture.

They are then placed in boiling water or steamed for three-quarters of an hour. By means of a knife, which has been sterilized in a flame, they are then cut into halves and placed in a large moist chamber or suitable

pan provided with a lid. The bottom of this vessel should first be covered with a piece of filter paper which has been moistened with water or with mercuric chloride solution. The cut and sterile surface of the potatoes can then be inoculated with the organisms to be cultivated, either by spreading the material over the potato with a sterile knife or by making parallel streaks. Inasmuch as there are several sources of contamination in this method, it has been largely displaced by the modified procedures.

In Esmarch's modification the potato is pared and cut into slices about a third of an inch thick, which are placed into small glass dishes about 7 cm. in diameter and 1 cm. high, known as Esmarch dishes. These are then sterilized by steaming in the usual way.

The best way of using potatoes for culture purposes is that introduced independently by Bolton and Globig. The cleaned potato is placed in boiling water for about half an hour. By means of a cork-borer or a test tube the end of which has been cut off, cylinders of potato may be punched out. The skin is removed from the ends of the cylinders, after which these are halved by a diagonal cut. The wedge-shaped semicylinders are now placed in sterile test tubes and sterilized by steam.

Another method which possesses certain advantages over the above consists of taking a large uncooked potato, punching out cylinders, and cutting wedges as just mentioned. These wedges are placed in a suitable vessel and tap water is allowed to flow over them about twenty-four hours. This removes certain soluble constituents of the potato, which if allowed to remain might discolor the finished medium after it has stood for some time. Also, the washing removes much of the acid which fresh potato contains. After removing the washed potato wedges from the running water, they are placed in Roux tubes and autoclaved at 120° C. for fifteen minutes. This cooks the potato and also sterilizes thoroughly.

Roux introduced a very useful modification of the test-tube method. A constriction is made in the lower part of the tube, about an inch from the bottom. This compartment may be filled with water or, when cultivating the tubercle bacillus, with five-per-cent. glycerin. These tubes can be readily prepared from the ordinary test tubes. A narrow blast flame is directed horizontally against the tube, which is rotated in a vertical position. The Roux tube is shown in Fig. 5070. A good substitute for this tube may be made by placing on the bottom of the test tube a layer of absorbent cotton, which may be soaked with the glycerin solution.

Glycerinated potato may be prepared by soaking the thoroughly washed, prepared potato wedges (see above) in a twenty-five-per-cent. solution of glycerin, from one-quarter to one-half hour. Then they are placed in tubes and autoclaved at 120° C. for fifteen minutes.

Mashed potatoes spread over the bottom of a flask have been used, but this offers no special advantage over the methods given. The preparation of potato gelatin with or without potassium iodide has already been described.

Bread Medium.—Ordinary bread is toasted to a crisp, then powdered, in which condition it may be kept in stock. For use the powder is placed on the bottom of small flasks and thoroughly moistened with water, then sterilized by steaming. This medium is particularly useful for cultivating moulds.

Plant Infusions.—These are useful for growing certain bacteria and also amebae. Infusions of hay, straw, fruits, grains, etc., take the place of meat extract. By the addition of agar or gelatin, solid media may be prepared. Beer wort, either as such or as a gelatin, is valuable for the cultivation of yeasts.

Protein-free Media.—With the exception of urine all the media described thus far contain some proteid matter. The latter, however, is not essential, for it is possible to grow bacteria on media which contain sulphur, nitrogen, and phosphorus in inorganic combination. Such a solution was used, for instance, at a very early

date by Pasteur. It consisted of 1 part of ammonium tartrate, 10 parts of candy sugar, the ash of 1 part of yeast, and 100 parts of water. The botanist Cohn employed a similar solution, consisting of 0.1 gm. each of potassium phosphate and magnesium sulphate, 0.01 gm. of tribasic calcium phosphate, 0.2 gm. of ammonium tartrate, and 20 c.c. of distilled water. Naegeli's solution was made by adding 1 gm. dibasic phosphate, 0.2 gm. magnesium sulphate, 0.1 gm. calcium chloride, and 10 gm. of ammonium tartrate to 1,000 c.c. of distilled water.

After the lapse of many years these non-albuminous fluids were again brought into use in a modified form by Uchinsky. His solution consisted of: Water, 1,000 parts; glycerin, 30-40 parts; sodium chloride, 5-7 parts; calcium chloride, 0.1 part; magnesium sulphate, 0.2-0.4 part; potassium phosphate, 2-2.5 parts; ammonium lactate, 6-7 parts; sodium asparaginate, 3-4 parts.

Fraenkel's modification of this solution contains 5 gm. of sodium chloride, 2 gm. of potassium phosphate, 6 gm. of ammonium lactate, and 4 gm. of sodium asparaginate. These substances are dissolved in 1,000 c.c. of water and the solution is then rendered slightly alkaline.

Similar solutions have been used by Maassen and by others. Thus Proskauer and Beck cultivated the tubercle bacillus on the following solution: Commercial ammonium carbonate, 0.35 per cent.; potassium phosphate, 0.15 per cent.; magnesium phosphate, 0.25 per cent.; glycerin, 1.5 per cent.

For cultivating the nitrous and nitric-acid organisms Winogradsky employed wholly inorganic solutions. The nitric-acid producers were grown in a solution consisting of 1,000 c.c. of water, 1 gm. potassium phosphate, 0.5 gm. magnesium sulphate, 0.01 gm. calcium chloride, 2 gm. sodium chloride. This is filled into flasks in portions of 20 c.c. each, together with a little freshly washed magnesium carbonate. To these flasks, after sterilization by steam, 2 c.c. of a two-per-cent. solution of ammonium sulphate is added, after which they are incubated to eliminate contaminations.

For the nitrous-acid organisms the solution consists of 1 gm. ammonium sulphate, 1 gm. potassium sulphate, and 1,000 c.c. of water. It is filled into flasks, magnesium carbonate added, after which they are sterilized by steam.

As a substitute for gelatin Winogradsky employed silicic-acid jelly, which was added to solutions of essentially the same composition as those just given.

Standardization of Media.—The procedure as introduced by Koch, and still followed in many laboratories, is to add a saturated solution of sodium carbonate, in portions of a cubic centimetre or more, to the nutrient medium, to be neutralized until a drop of the mixture, transferred by means of a glass rod, turns red litmus paper promptly blue. In some laboratories a strong solution of sodium hydrate is used in the same way. Obviously this method lacks quantitative precision, and the duplication of the same reaction in several batches of material is out of question. Moreover, it is an established fact that the reaction of a medium has a very important influence upon the development of bacteria. For these reasons the bacteriological committee of the American Public Health Association, adopting Fuller's work, recommended the following method for the titration of nutrient media. The reagents necessary are:

1. Five-tenths-per-cent. solution of phenolphthalein in fifty-per-cent. alcohol.
2. Normal sodium hydrate (N. NaOH). A litre of this solution contains 40 gm. of NaOH.
3. Twentieth normal sodium hydrate ($\frac{N}{20}$ NaOH). A litre of this solution contains 2 gm. of NaOH.
4. Normal hydrochloric acid (N. HCl). A litre of this contains 36.5 gm. HCl.
5. Twentieth normal hydrochloric acid ($\frac{N}{20}$). A litre of this contains 1.825 gm. of HCl.

The preparation of these solutions requires some fa-

miliarity with the methods of quantitative analysis. The solutions can be built up by starting from a twentieth normal solution of oxalic acid or, better, succinic acid.

The titration is carried out as follows: To 5 c.c. of the filtered medium in a six-inch porcelain evaporating-dish add 45 c.c. of distilled water and 1 c.c. of the phenolphthalein solution; boil for three minutes to expel carbonic acid, then run in the twentieth normal alkali, drop by drop, with constant stirring, until a bright pink color results. The number of cubic centimetres of the twentieth normal alkali required to neutralize 5 c.c. of the medium gives directly the number of cubic centimetres of normal alkali (i.e., percentage) required by 100 c.c. of the medium. Thus if 5 c.c. of the medium requires 2.8 c.c. of $\frac{N}{20}$ alkali, then 100 c.c. would need 56 c.c. $\frac{N}{20}$, or 2.8 c.c. of N. NaOH.

The quantity of the medium remaining is now measured and the amount of alkali needed for neutralization is calculated and added. After the addition of the alkali the liquid is boiled and a portion is then titrated as before. It should be neutral, and if it is not, as often is the case on account of unknown changes, the requisite amount of alkali to make it so is added to the bulk.

The medium which is neutral with reference to phenolphthalein is very alkaline with respect to litmus. Thus a bouillon which is neutral to litmus will require about 25 c.c. of normal alkali per litre to make it neutral to phenolphthalein. In general the addition of 10 c.c. of normal alkali to a medium which is neutral to litmus imparts the most favorable degree of alkalinity. Hence the optimum reaction with reference to phenolphthalein is obtained by adding 15 c.c. of normal acid to the litre of neutralized medium. It is customary to use the sign + to indicate an acid reaction, and that of — for one that is alkaline. Thus + 15 means that the reaction is acid with respect to phenolphthalein, and that one litre of the medium would require 15 c.c. of normal alkali for neutralization.

The titration with litmus as an indicator is best carried out in the following way: Portions of 5 c.c. of the medium are measured out into each of four or five large test tubes. In the case of bouillon the amount of $\frac{N}{20}$ alkali needed to neutralize this amount may vary from 0.3 to 0.6 c.c. Hence to tube 1 add 0.3 c.c.; to tube 2 add 0.4 c.c.; to tube 3 add 0.5 c.c., etc. The contents of each tube are then boiled for a minute, after which a slip of red and one of blue litmus paper are dropped into the hot liquid and allowed to remain there for about a minute. The papers are then drawn out, side by side, on the walls of the tube when the colors can be compared. In this way the amount of alkali necessary to neutralize 5 c.c. with respect to litmus can be determined. Bouillon, as well as agar, usually requires about 5 c.c. per litre for neutralization, while gelatin needs from 30 to 35 c.c. Having determined the amount needed for neutralization, this amount, together with an excess of 10 c.c. per litre, to impart a suitable alkaline reaction, is then added to the medium.

For ordinary purposes it is hardly necessary to resort to these rather complicated methods. It is sufficient to add directly to bouillon and to agar 15 c.c. of normal alkali per litre. Gelatin will require about 40 c.c. In general, sodium carbonate is preferable to the hydrate.

Preparation and Filling of Tubes.—The cheaper grades of test tubes should be avoided. They are very thin and therefore break easily, and, moreover, on heating they will often frost because of the separation of silicic acid. The best test tubes are the "blue-lined" or "resistant glass" quality, or those of genuine Bohemian glass. The size used varies with the purpose and the individual taste; 12 × 125, 15 × 150, and 20 × 150 mm. are convenient.

The new tubes of the better glass can be used after being swabbed out with warm water.

The cheaper grades are very alkaline, and for that reason should be first soaked in very dilute warm hydrochloric acid, after which they should be rinsed or swabbed

thoroughly in clean warm water. The cleaned tubes are allowed to drain, and when dry are plugged. Used tubes should be sterilized by steaming for a half-hour after which they may be filled with water and again heated, so as to bring the more or less dried contents into solution.

The simplest way of plugging is to place over the mouth of the tube a piece of cotton, about two inches square, which is then pushed within by means of a narrow glass rod or a pair of smooth forceps. Such plugs answer all ordinary purposes. They are, however, rather loose, and permit evaporation of the media, and cannot be used when the tubes are to be sealed with wax. A firm solid plug is made by taking a piece of cotton, about three inches square. This is folded into thirds and then rolled up from the end into as firm a cylinder as possible. By a twisting motion the plug is inserted into the tube, and only enough cotton is left on the outside to permit grasping of the plug. The plugged tubes are then placed in a wire basket, such as is shown in Fig. 5071. These baskets are made of heavy galvanized netting. The usual size is 24 cm. high and 18 cm. square. Smaller baskets, 10 × 12 and 18 cm. high, are very useful. Circular baskets, of a size to fit the sterilizer, are also used.

Flasks, bulbs, etc., should be prepared for sterilization in the same way.

After the tubes have been sterilized by heating in the dry-heat oven at 150° C. for one hour, they are ready to be filled with the nutrient media. This can be done by the aid of a small funnel. When large quantities of media are to be tubed much time can be saved by using a large funnel or globe receiver, such as is shown in Fig. 5072. The lower end of the bulb is connected with a drawn-out glass tube and is provided with a pinch-cock. In this way the media can be rapidly filled into the tubes.

Another simple method consists in using the ordinary Florence flask, containing the medium and securely fitting a two-bore rubber stopper in its mouth. Through one of the openings pass a straight thistle tube, of such length that it almost touches the bottom of the flask, and plug the external bulbular portion with cotton to act as an air filter. Through the second opening pass a straight glass tube about 10 cm. long so that it projects from 2 to 3 cm. into the neck of the flask. To this tube attach a drawn-out glass tube, by means of a piece of rubber tubing, to permit the use of a pinchcock. For filling test tubes the flask is inverted, and supported neck downward in a ring retort-stand of suitable size. This simple apparatus admits of complete sterilization intact

FIG. 5072.—Globe Receiver for Filling Media into Tubes, with Burette Attachment. (Novy.)

together with the medium. But in such case the pinch-cock must first be removed to allow air or vapor a means of escape from the flask during the heating. By this method a sterile medium is ready for use as soon as prepared.

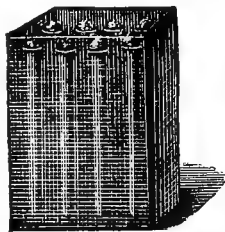


FIG. 5071.—Wire Basket for Sterilizing Tubes.

Ordinarily the tubes are filled to the depth of one and one-half or two inches. In special cases in which definite quantities are desired, the simple apparatus shown in Fig. 5072 can be used. The containers, with the media to be filled, can first be sterilized by steaming, after which the media can be measured out into sterile tubes, which will not require further treatment. A less desirable apparatus is that of Treskow, shown in Fig. 5073.

STERILIZATION.—By sterilization is meant the total destruction or removal of all organisms in or about a given object. This can be accomplished in a variety of ways.

1. *By Direct Flaming.*—This method is applicable for the sterilization of glass rods, slides, cover-glasses, platinum wires, searing irons, and rough instruments. Valuable surgical instruments would of course be damaged by this procedure.

2. *By Means of the Dry-heat Sterilizer.*—The form most often used is that of Koch, shown in Fig. 5074. This is made of sheet iron, is double walled, and the outer wall may be lined to advantage with thick asbestos board. The form as shown is designed to sterilize not only tubes and flasks but also glass tubing, pipettes, and the like. The oven is used for sterilizing only glass and metal ware. It must not be used for sterilizing media. A temperature of 150° C. should be maintained for one hour. Usually it will be sufficient to allow the temperature to rise, and as soon as it has reached 200° the gas is turned off. The cotton should show a slight tinge of yellow after this heating. If the plug browns considerably and powders it is due more to the fact that the cotton has been chemically treated than to the heat.

3. *Fractional Sterilization at 56°–58° C.*—This method was introduced by Tyndall, and has been used for the sterilization of liquid serum, milk, and other fluids which are liable to be altered more or less by heat. It is based upon the fact that the actively vegetating forms of bacteria are readily destroyed as a rule by exposure for some minutes to this temperature. The resting forms or spores are not in the least affected by such exposure. It is necessary to wait until the spores have germinated into the vegetating forms, which can then be destroyed by a second like heating. As ordinarily practised, the method is as follows: The tubes are placed in an apparatus, such as that shown in Fig. 5075, and are heated for one hour at the given temperature on each of seven or eight consecutive days.

This method sometimes gives good results, at other

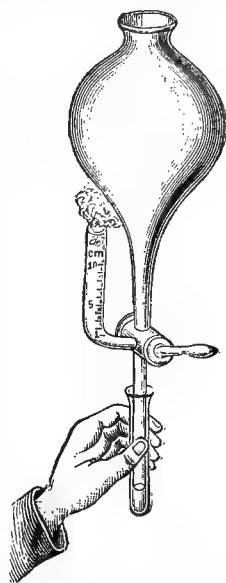


FIG. 5073.—Treskow's Apparatus for Measuring Media into Tubes.

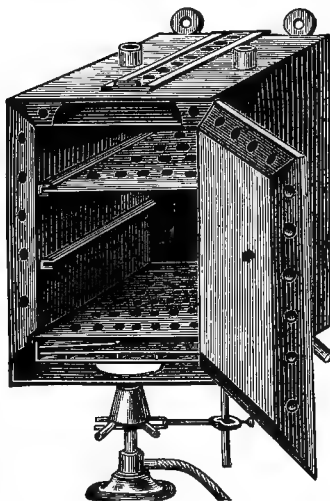


FIG. 5074.—Koch's Dry-Heat Sterilizer.

times it fails. The reason for this lies in the presence or absence of the so-called thermophilic bacteria. These organisms actually grow best at the temperature em-

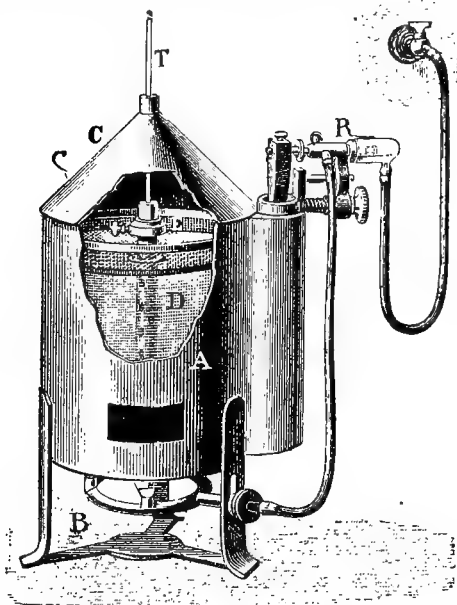


FIG. 5075.—Roux Water-Bath for Sterilizing Serum with Metallic Regulator.

ployed, and hence, if they chance to be present, the method is inapplicable. A temperature of 70°C . may be used in like manner, but this causes coagulation of the serum.

By pasteurization is meant the partial destruction of the organisms which are present in a milk. This is accomplished by exposing the milk for half an hour, or more, to a temperature of about 68°C . (155°F). While this temperature does not destroy the spores which

may be present, it does kill the lactic acid and other bacteria, which do not produce spores. As a result, milk treated in this way will keep for several days without coagulating. If a higher temperature is used, the taste of the milk is likely to be impaired.



FIG. 5076.—Koch's Steam Sterilizer.

3. *Sterilization in Flowing Steam.*—Several forms of apparatus have been devised for this purpose. Among the earliest is the well-known form which bears Koch's name. This apparatus is used almost entirely in Ger-

many, and to a considerable extent in this country. It is shown in Figs. 5076 and 5077.

It consists of a cylinder of galvanized iron, or better of copper, which can be given such dimensions as may be desired. Ordinarily it is about half a metre high and about 25 cm. in diameter. It is surrounded by a thick covering of felt *M*, to prevent loss of heat by radiation. In the interior of the cylinder at *R* is placed a grate which serves as a support for the pail and other vessels to be disinfected. The water in the lower compartment is heated by one or more large gas-burners. Above it is closed with a cover *D*, which is also covered with felt. A central opening permits the escape of steam, and can be used for the insertion of a thermometer. The pail shown to the right of the sterilizer has a grating for a bottom, to allow free access of the steam, and in it are placed the articles to be sterilized.

The nutrient media are as a rule sterilized by steam. A single heating for one hour in steam at 100°C . is usually sufficient to render the media sterile. Prolonged heating, however, tends to alter the media, and for that reason fractional or discontinuous sterilization is resorted to. The latter has the additional advantage that it renders the medium more surely sterile. There are spores which can withstand steaming for one and even five or six hours, and if such forms chance to be present it is evident that the material cannot be sterilized by the single heating for one hour. In the other procedure the media are steamed for fifteen minutes or half an hour, according to the nature of the medium, on each of three consecutive days. The first heat serves to destroy the vegetating germs that may be present. In the interval which elapses between the first and second heating, the spores which are probably present will

germinate and are thus converted into the much weaker form, which is then destroyed by the second steaming. The second interval allows any remaining spores, which may have failed to germinate the first day, a chance to do so, and the third heating is expected to dispose of these last organisms. As a rule all media should be incubated for one or two days to make sure that they are perfectly sterile.

If any growth develops in the tubes or flasks these should be discarded, and only those which are free should be preserved for use.

Failure to secure sterilization by this procedure is

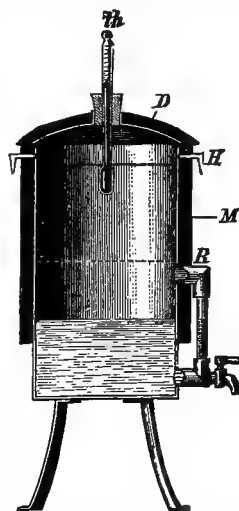


FIG. 5077.—Section of Koch's Steam Sterilizer.

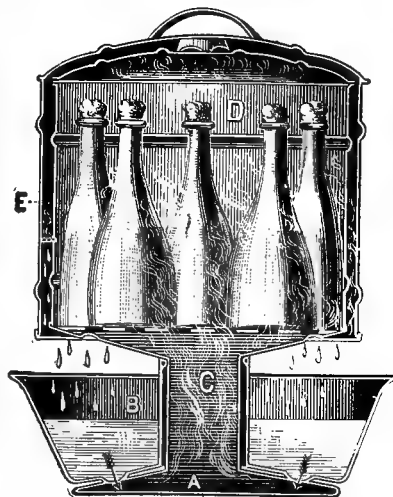


FIG. 5078.—Arnold Steam Sterilizer, Sectional View.

due to one of the following conditions: The temperature which prevails during the twenty-four-hour period which elapses between the consecutive heats may be so high that the spores which are present not only germinate, but the vegetating forms in turn give rise to spores, so that a larger number of resistant forms are present on the second or on the third day than were present in the beginning. Again, it may happen that the temperature is too low, in which case the spores cannot germinate, and hence will be found to resist sterilization. Another source of error, though much less common, was pointed

The tubes filled with media are placed in the pail, and this is then set on the water-bath, the water of which has been previously raised to active ebullition. In a few minutes steam will issue from the tube in the top of the cover. It is always advisable to take the temperature of the vapor as it issues from a sterilizer and to count the time of exposure from the moment that the vapor actually shows the temperature of steam, that is 100° C.

4. *Sterilization by Steam Under Pressure.*—This procedure is used almost entirely by the French workers. Its usefulness is such as to merit a wide introduction into this country. The apparatus, which is designated as an autoclave, is shown in Fig. 5080. It consists of a strong boiler, in the bottom of which a small quantity of water is placed. The articles to be steamed are placed in a wire basket, which is set on the bottom of the boiler. The lid is closed with a rubber gasket and securely held in place by thumb-screws. Inasmuch as the amount of aqueous vapor in a given space, as well as the temperature, in the case of confined steam, is greater than with flowing steam, it follows that the autoclave is considerably more efficient. Thus steam at 130° C., under pressure, will destroy instantaneously spores which would resist flowing steam at 100° for five or six hours.

The culture media can be sterilized by a single heating for fifteen to thirty minutes at 110° C. A higher temperature should be avoided, as it tends to alter the reaction of the media. Glass apparatus, filters, rubber, etc., can be sterilized by heating at 120° for half an hour. Infected animals can be subjected to 120° for the same length of time, or to 130° or more for a less period.

It must be remembered that the autoclave requires more care than an ordinary sterilizer owing to the danger of explosion. The following points should be observed in its use: Enough water should be present; after the burners are lighted, the steam valve should be left open until all the air has been expelled; when the steam has flowed rapidly for one or two minutes the valve is closed; as soon as the desired temperature is indicated on the gauge, the burners are turned down, so that this temperature is maintained for the required time; the burners are then turned off, but the steam valve is not opened until the temperature has fallen below 100°, after which the lid can be removed. The safety valve should be tested to open at about 125° C. It is a good rule not to leave the autoclave out of sight while the temperature is rising.

Obviously this piece of apparatus can also be used as a steam sterilizer with temperature at 100° C. In such case the steam valves above are opened and the water is heated to the boiling-point. If steam is generated more rapidly than it can make its exit, the pressure rises, consequently the temperature goes above 100° C. Therefore boil gently or raise cover enough to allow free escape of the steam.

5. *Sterilization by Filtration.*—It is possible to remove completely all the organisms which may be present in a liquid by filtration. Filter paper, of course, on account of the small size of the bacteria, cannot be used for this purpose. There are only two reliable filters for bacteriological work. That known as the Pasteur-Chamberland filter is the best, and is made of unglazed porcelain. The form as used for filtering water for domestic use is shown in Fig. 5081. The original French filters are to be preferred to the German imitations. They are made in two grades; that marked *F* is more porous than that marked *B*.

The Kitasato filter, a narrow form of the above, is also made of unglazed porcelain, and is intended for the fil-

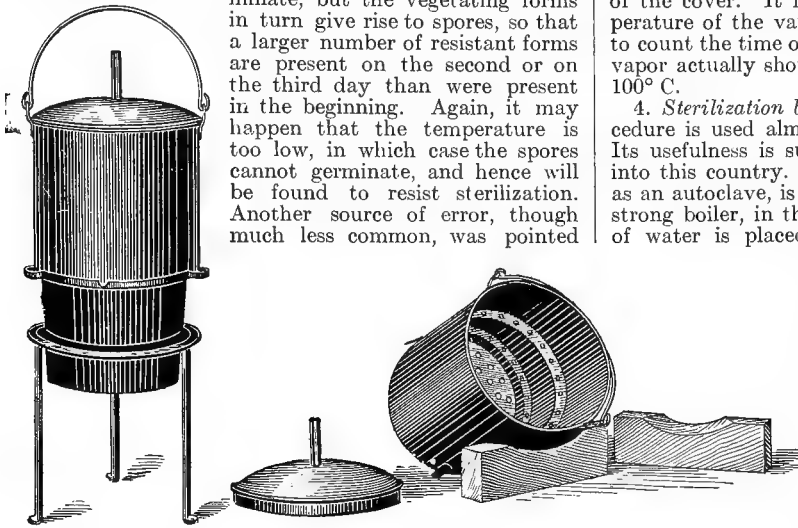


FIG. 5079.—Navy Steam Sterilizer.

out by Smith. If the spores of anaërobic bacteria are present in a bouillon, they cannot from their very nature germinate under the ordinary conditions, that is, in the presence of the air, and may therefore escape destruction.

In this country, and even in Germany, the Arnold steam sterilizer has met with a very favorable reception. The apparatus is shown in Fig. 5078. It consists of: (a) a flat, shallow boiler, holding but a small amount of water, and therefore requiring but a minimum amount of heat to produce steam; (b) a reservoir placed upon the boiler, which it constantly feeds and insures the constant formation of steam; (c) a covered steam chest or receiving vessel, placed above the reservoir and connected with the boiler by a cylindrical tube of large diameter; and (e) a hood, covering the receiver and enclosing an air space, which is constantly supplied with escape steam. The hood and the steam jacket which it encloses prevent variations in temperature in the receiving vessel so long as the heat applied to the boiler remains unchanged.

A cheap and thoroughly efficient steam sterilizer adapted for individual work is shown in Fig. 5079. This consists of an ordinary Hoffmann iron water-bath

FIG. 5080.—Chamberland Autoclave for Sterilizing by Steam under Pressure. (Novy).

10–20 cm. in diameter. On this is placed a copper pail (20 × 20 cm.), which is provided with a perforated bottom. Two perforated rings on the inside allow the passage of steam, and prevent the cotton of the tubes from coming into contact with the side of the steamer.

tration of very small amounts of liquid. This can, however, be done also with the larger filter. It is shown in Fig. 5082.

The Berkefeld filter (Fig. 5086) consists of closely packed infusorial earth. It can be obtained in several sizes, having the general shape of the Chamberland - Pasteur bougie. It is considerably more porous than the porcelain filter, and is therefore adapted for rapid filtration, but it should be borne in mind that it is more likely to allow the passage of bacteria.

A useful form of apparatus for holding the Pasteur-Chamberland bougie, that of Martin, is shown in Fig. 5083. It consists of a metal cylinder with a funnel-shaped top, which permits the filtration of the culture through filter paper previous to its passage through the bougie, and thus obviates or lessens the clogging of the latter. A rubber ring serves to make a tight joint when the bougie is held in place by the lower screw cap. The lower end of the bougie is connected with a piece of vacuum rubber tubing to a globe receiver. The entire apparatus is sterilized by heating in an autoclave. The filtration may be carried on by gravity, or an aspirator may be connected with the upper tube of the globe receiver. When the filtrate is to be transferred, the drawn-out side tube is scratched near the end with a file, and then broken off, after which the tube is flamed and the liquid is drawn off into sterile tubes or flasks. This globe receiver can be used until the drawn-out tube is too short, when a new tube is fused on.

A better form of a globe receiver is shown in Fig. 5086. This is provided with three side tubes, which are plugged with cotton, after which the receiver is sterilized in a dry-heat oven. When it is to be used, the cotton is removed from the tube *D*, which is then connected with the sterile bougie by means of a piece of sterile vacuum tubing. The horizontal tube *F* is similarly connected with the sterile drawn-out glass tube *G*. The tube *E*, with its cotton plug in place, is connected with a Chapman pump. The filtrate may be withdrawn by means of a sterile bulb pipette, or in the same way as from the receiver of Martin. The advantages in the short rubber tubing, compactness, and the convenience in attaching the drawn-out tube. This vacuum receiver can be obtained in several sizes, such as one-quarter, one-half, one and one and one-half litre capacity.

Instead of a metal cylinder to hold the bougie, Novy has devised one of glass. This is shown in Fig. 5084. The necessary tight joint between the bougie and the glass cylinder is made with a rubber ring, and the bougie is brought up tight into place by means of small vises, which act on the flange and on an iron washer. The arrangement is shown in Fig. 5085. If desired the liquid can be filtered under pressure, in

glass cylinder by means of a rubber and iron washer and the clamps mentioned (Fig. 5086). A more convenient arrangement is to use a cylinder of brass of suitable length and width, threaded at each end. The lower end is provided with a screw cap, through which the metal end of the Berkefeld bougie is passed. The upper end is also closed with a screw cap, provided with a three-eighths of an inch nipple, which serves to connect the cylinder with the compressed air. The tip of the Berkefeld is connected with a globe receiver. The filtration can then be carried out by gravity, by aspiration, or by pressure.

The filtration of liquids constitutes an exceedingly important part of bacteriological technique. By its means the soluble products of bacteria may be separated from the solid cells. In this way the toxins of many pathogenic bacteria are prepared. Again it is by the filtration process that it has been possible to demonstrate the existence of the so-called ultramicroscopic organisms. While the common bacteria will not pass through a filter, there are a number of diseases in which the cause is so minute that it will go through the Berkefeld, and, at times, even through the Pasteur-Chamberland bougie. Yellow fever, sheep pox, foot-and-mouth disease, contagious pleuro-pneumonia of cattle, chicken pest, rinderpest, horse sickness, molluscum contagiosum of birds, and the "mosaic disease of tobacco" are of this class; so also is that of rabies. The fact that a given filtrate infects is not proof that the cause is always in this extremely minute form. It may be that the real organism is relatively large, as in the case of the rat trypanosome, and yet Berkefeld filtered cultures of this will often infect animals. This is due to the existence of a minute stage in the development of the organism. It is therefore to be expected

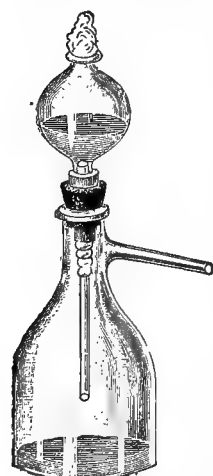


FIG. 5082.—Kitasato's Filter.

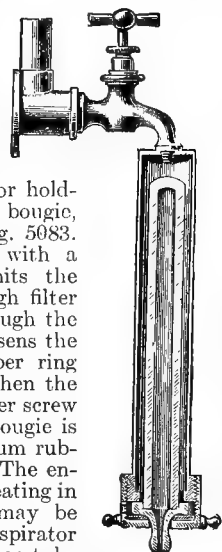


FIG. 5081.—Pasteur-Chamberland Filter.

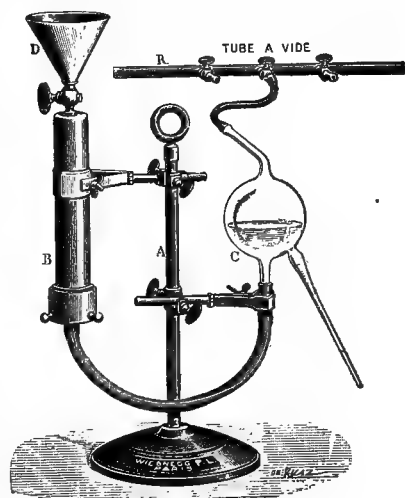


FIG. 5083.—Martin's Filter.

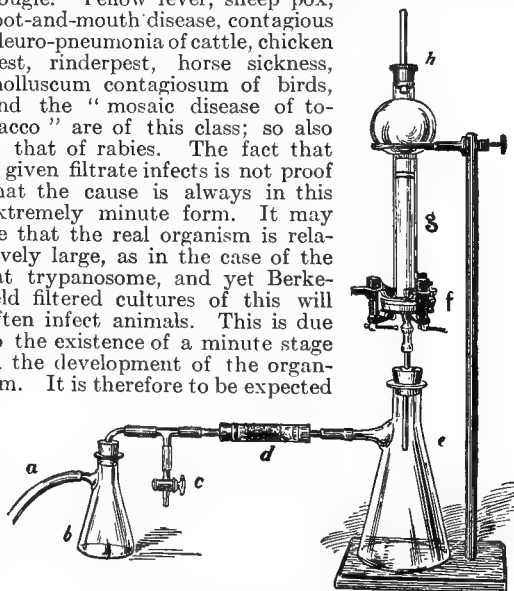


FIG. 5084.—Novy's Filtering Apparatus.

that the pathogenic protozoa, though they themselves may be large, may give rise to filterable sporozoites.

6. *Sterilization by Chemicals.*—This principle is applicable only to a limited extent to nutrient media.

The addition of such substances as carbolic acid or mercuric chloride will serve to destroy the organisms which may be present; but since these compounds cannot be

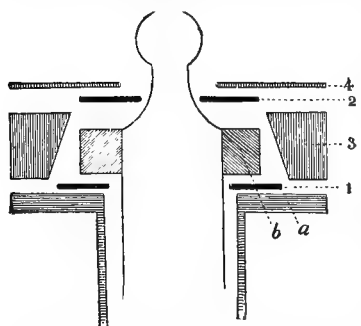


FIG. 5085.—Connections for the Novy Apparatus. 1, 2, 3, Rubber rings; 4, iron washer.

removed from the medium, it follows that it cannot be used for culture purposes. A few substances have, however, been used with this object in view. Thus if chloroform is added to milk or blood serum, and is allowed to act long enough, it will bring about sterilization. The remaining chloroform can finally be driven off by means of gentle heat and by

aëration. Ether has been used in the same way, and indeed this is a useful procedure for sterilizing such weak cultures as those of cholera. Glycerin, as is well known, is added to vaccine with the object of destroying the common pus-producing organisms which are so often present. It certainly will in time destroy all of these accidental bacteria, but, unfortunately, prolonged exposure of the vaccine virus to the glycerin damages it as well.

Chemical disinfection of drinking-waters has also been proposed, especially in connection with military operations. For this purpose various substances, such as bromine and the organic peroxides, have been suggested.

In the laboratory this method is resorted to more or less to sterilize old used cultures, test-tubes, and even animals. Five-per-cent. carbolic acid or 0.1-per-cent. mercuric chloride is employed.

The Incubator.—It is customary to divide bacteria into two large groups—the saprophytic and the parasitic—according as to whether they grow in nature on dead matter or in the living body. Among the latter are classed the disease-producing bacteria. In general the optimum temperature for the growth of the saprophytic organisms is about 25° C. (77° F.), whereas the pathogenic bacteria thrive best at the temperature of the body. In order to supply this requirement it is necessary to use an incubator or thermostat, the temperature of which can be maintained without variation at any desired level. Various forms of apparatus have been devised for this purpose; that of Koch is shown in Fig. 5087. It consists of a double-walled box of copper, the sides and

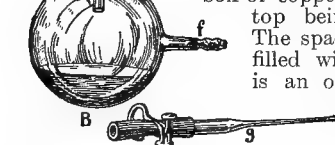


FIG. 5086.—Berkefeld Filter showing Manner of Attachment. Globe receiver. (Novy.)

top being covered with felt. The space between the walls is filled with water. In the top is an opening communicating with the interior air space, and in it a thermometer is placed to indicate the temperature. The openings in the corners communicate with the water space. One of these is intended to hold a thermo-regulator, while the other serves for the addition of water. Inner and outer doors are provided, and in the better

models provision is made for ventilation and for keeping the air moist.

The apparatus may be heated with an Argand burner. The ordinary Bunsen burner is not used because of the danger of "shooting back." The Koch safety burner is

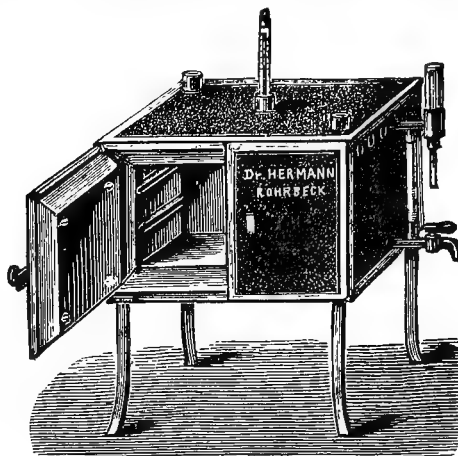


FIG. 5087.—Koch's Incubator.

to be preferred, for it automatically shuts off the supply in case the gas should by any chance happen to be turned off. It consists of two iron spirals which, as they are heated, expand, and in so doing communicate this motion to an arm which then swings under and supports the weighted lever of the valve. If by any accident the flame should become extinguished, the spirals cool and contract; this causes the supporting arm to swing out from under the lever, which then falls and thus shuts off the gas (see Fig. 5088).

In case gas is not available the incubator is heated with an oil lamp. The Sartorius model is especially well constructed for this form of heating. A good substitute can always be found in the ordinary egg incubator. In a few places the heat is supplied by means of electric hot plates.

By far the most important accessory to an incubator is a thermo-regulator, which will automatically control the supply of gas and hence the temperature of the oven. Several of the more common forms are shown in Fig. 5089. The Reichert form, though very widely used, is far from being the most satisfactory. The lower bulb is filled with mercury, which as the temperature rises

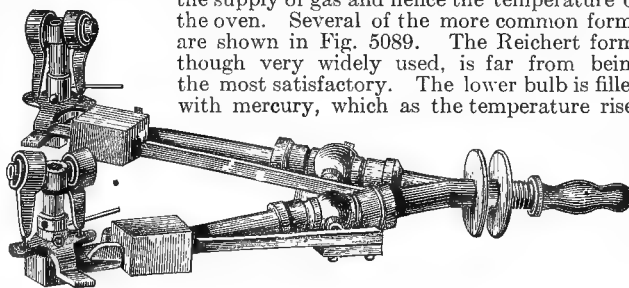


FIG. 5088.—Koch's Safety Burners.

shuts off the opening through which the gas enters. In order to prevent the flame from being extinguished a minute opening is made in the gas-delivery tube whereby a minimum flame can be maintained.

In the Bunsen form the lower compartment is nearly filled with a mixture of equal parts of ether and absolute alcohol, after which a sufficient quantity of mercury is added to act as a valve. The upper part is closed with a stopper, through which passes the gas tube. When the proper temperature is reached, this tube is pushed down till the gas flame drops. The minimum opening prevents total extinguishment. By careful manipulation the regulator can be set at any temperature which may be desired.

In both the Novy and Dunham forms the lower bulb is filled with absolute alcohol. As this expands it acts against a column of mercury, which in turn shuts off the supply of gas. The lateral screw permits the adjustment of the regulator to the desired temperature. In the former the minimum supply can be regulated to a nicety. This enables it to be used for a water-bath, or for a small or large incubator. It can be obtained with the alcohol cylinder of different sizes, according to the use for which the apparatus is intended.

The metallic regulator of Roux is intended for controlling the temperature of large water-baths and of incubator-rooms, for which pur-

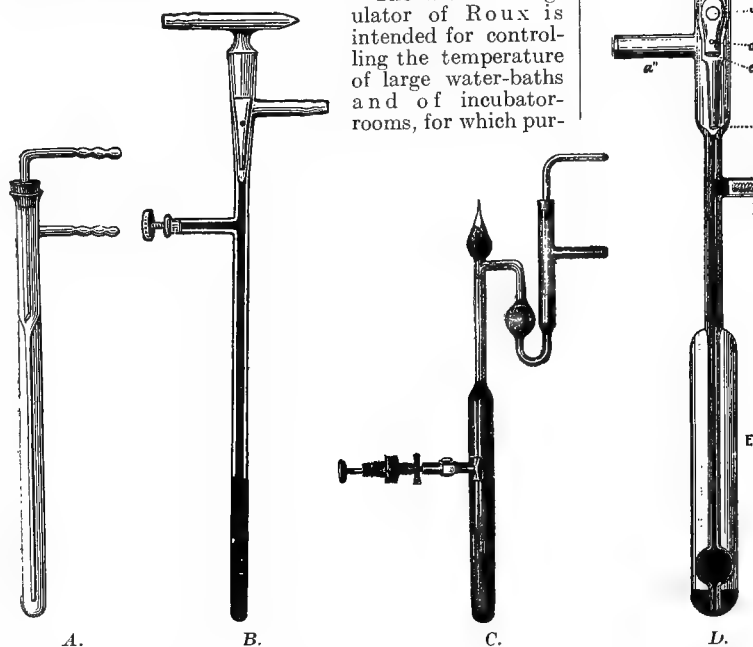


FIG. 5089.—Thermo-Regulators, A, Bunsen's; B, Reichert's; C, Dunham's; D, Novy's.

pose no better device can be found. It is made in the two forms, the straight and the U shape, shown in Fig. 5090. It consists of two metal bands having different coefficients of expansion. These are soldered together the full length. As the temperature rises, the free upper arm moves from and thus releases a spring valve, which shuts off the main supply of gas. A minute opening serves to supply a minimum amount of gas, and thus prevents extinguishment of the flame.

The incubator described in its several modifications answers all ordinary purposes. In large laboratories they can, however, be dispensed with almost entirely, and their place is taken by the incubator-room. By this is meant a room, usually about eight feet cube, which is maintained at a constant temperature. This arrangement was first employed at the

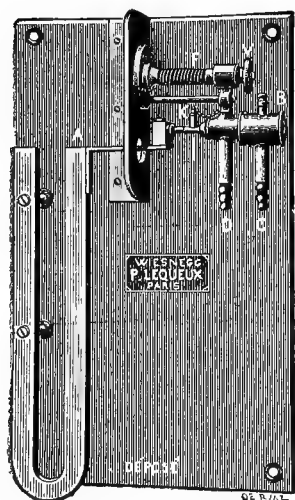
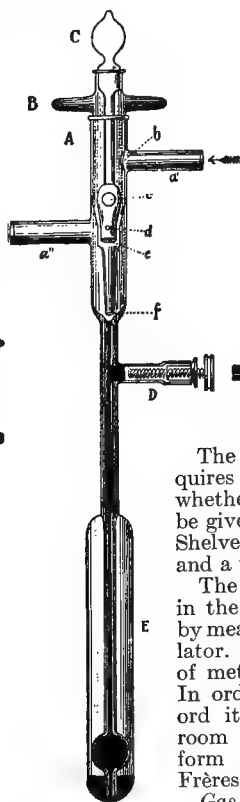


FIG. 5090.—Roux Metallic Thermo-Regulator.

Pasteur Institute, where the heat is conveyed to the room by means of large pipes along the wall, filled with water, or better with glycerin. The circulating liquid is

heated by a small gas stove placed on the outside of the room.



The construction of the room requires no special care. The walls, whether of brick or of plaster, should be given several coats of white zinc. Shelves, water, gas and electric light, and a window should be provided.

The regulation of the temperature in the rooms heated by gas is done by means of the Roux U-shaped regulator. All the connections should be of metal to lessen the chances of fire. In order to have a temperature record it is advisable to place in the room a thermo-metrograph, the best form of which is made by Richard Frères, of Paris.

Gas-pressure Regulator.—The best results with any form of thermo-regulator are obtained when the gas pressure is constant or nearly so. When the variation is considerable it is advisable to pass the gas through a pressure regulator before it reaches the thermo-regulator. There are several forms of apparatus for this purpose. The Moitessier regulator is shown in Fig. 5091. It consists of a cylinder A, which is filled to the level of G with a mixture of equal parts of glycerin and water. On this is floated the metal shell B. The gas is admitted to the interior of B, through the tube K, the pressure being indicated by the manometer P. The gas flows into B until it is filled, when it raises it up and shuts off the supply of gas by closing the valve D. The pressure on the burner is regulated by the weights placed in the pan H, which is connected with B by the rod G. The amount of pressure on the burner is indicated by the manometer on the left of the apparatus. The burner is connected with the apparatus by means of a rubber tube attached to I, and the height of the flame is regulated by the stopcock M.

A cheaper and more simple regulator is that devised in Novy's laboratory by Murrill and shown in Fig. 5092.

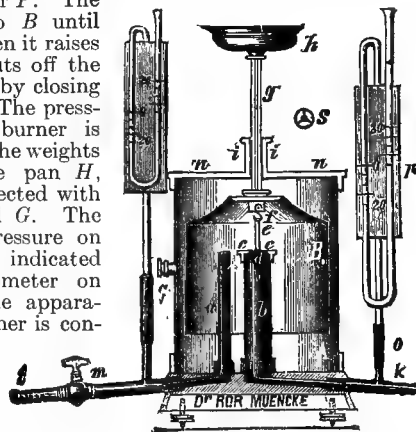


FIG. 5091.—Moitessier's Gas-Pressure Regulator.

The gas passes into a cylinder which floats in liquid petroleum and leaves by two tubes at the bottom, one of which is connected with the thermo-regulator, the other with a manometer. The cylinder is weighted so as to give the desired pressure to the out-flowing gas.

During the hot summer months it is desirable to have an apparatus which will keep a fairly constant low temperature, below that which would cause the gelatin cultures to melt. There are incubators constructed for this purpose which furnish a supply of ice-cold water when the temperature rises above a given point. If the temperature drops too low, the electric lamp is turned on.

When the temperature of the water as it leaves the ground is about 15° C. (59° F.) it is possible to use the simple apparatus shown in Fig. 5093. This is made of galvanized iron. The inner box is held in place by means of a couple of stout rods. The water enters at the bottom through the small tube, which stops short on the inside of the outer box. The water then flows under and around the inner box, and eventually reaches at the farther end the wide outflow tube. The end of this is turned up and is provided with a short piece of rubber tubing. By moving this up or down the level of the water in the box can be regulated. By regulating the flow of the water it is possible to maintain a fairly constant temperature in the inner compartment.

The Methods of Cultivation.—The fundamental basis of bacteriology may be said to be the fact that it is possible to cultivate artificially, and that in pure condition, nearly all of the known forms of bacteria. Until methods had been devised for this purpose it was not possible to determine definitely the part played by any organism either in the ordinary phenomena of fermentation or in the more mysterious processes of disease. To arrive at a demonstration of the causal relation of a given organism to the change which it is supposed to induce it is necessary to do two things: First, the or-

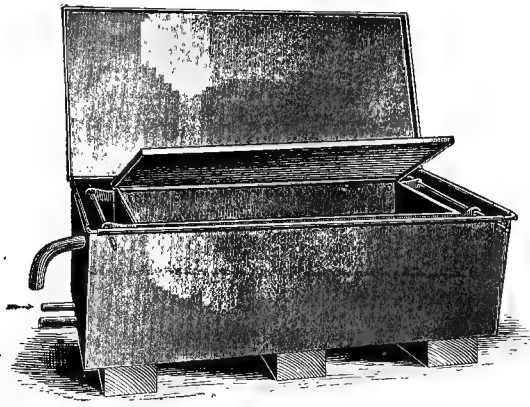


FIG. 5093.—Novy's Low-Temperature Incubator.

ganism must be isolated in pure culture; and second, the pure culture, once obtained, must be maintained by transplantation. The pure culture thus kept up through a series of transplantations, or generations as they are called, can then be tested upon animals to see if it will

reproduce the disease, or upon suitable media to ascertain if it will cause the kind of fermentation, the pigment, or the light which it is supposed to produce.

By a pure culture is meant one which is derived from a single cell. A given bacterium, small as it is, multiplies by division, and thus gives rise to two new individuals. These in turn grow and divide, yielding four cells. This process is kept up till many millions of organisms constitute the offspring of a single cell. Inasmuch as the division of bacteria is very rapid under favorable conditions, many dividing every half-hour, it follows that in a few hours a visible growth may be seen where at the beginning but a single cell was present. If the medium in which they are growing is liquid, it will usually become cloudy because of the disseminated bacteria.

The early methods of cultivation, as employed by Pasteur, made use of liquid media. Under these conditions it was exceedingly difficult to obtain pure cultures, and indeed it was largely a matter of chance and patience. Suppose that a given liquid contains two kinds of bacteria; in order to separate these so as to have a single cell as a starter for the pure culture it would be necessary so to dilute the liquid that in all probability a drop, or a cubic centimetre, would contain but one cell. This small quantity would then be taken and transferred to a sterile medium, and in this way it would be possible to obtain presumably pure cultures. Failure, however, was necessarily frequent and the element of doubt always remained.

The introduction of the nutrient gelatin by Koch made it possible to secure pure cultures with the greatest of ease. All that was necessary was to inoculate the liquefied gelatin with the mixture of bacteria, and after thorough agitation so as to separate each cell from its neighbor, to pour the liquid on to the surface of a sterile plate. The gelatin now solidifies, and imprisons, as it were, the separated cells. Each of these now multiplies and reproduces its kind; eventually, in the course of a day or two, a small growth, perhaps of the size of a small pinhead, appears. This is called a colony, and since it is derived from a single cell it constitutes a pure culture. Such is the principle of the dilution method for obtaining pure cultures. The isolation once accomplished, all that is necessary is to transplant the colony to sterile culture media so as to keep up the growth.

The transferring of bacteria is usually done by means of a platinum wire. The wire, which should be about two inches long and fairly stiff, about No. 21 in size, is fused into the end of a glass rod. According to the object in view it is either straight, bent, or is provided with a loop as shown in Fig. 5094.

At times a bunch of very fine platinum wires attached to a holder, the so-called Kruse's brush, is used to spread the material over the surface of the media. A glass rod bent at right angles is also very useful for this purpose. The Roux spatula of nickelled steel was first employed for the purpose of transplanting bits of diphtheritic membrane to the culture tube. A similar spatula made of thick iron wire is extremely useful for transferring moulds and compact growths, such as that of actinomyces. The Nuttall platinum spear is particularly useful for transferring, bits of tissue, blood, etc., to the nutrient media. These two instruments are shown in Fig. 5095.

FIG. 5092.—Murrill's Gas-Pressure Regulator. Cross-section. (Novy.)

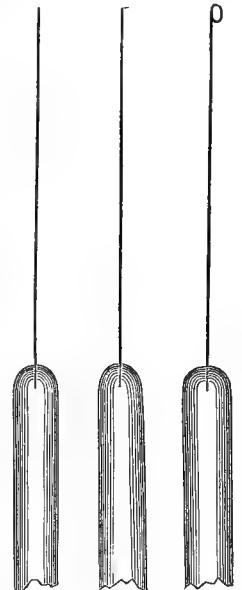


FIG. 5094.—Platinum Wires, Fused in Glass Rods.

The transferring of liquids, in large or in small quantities, can best be done by means of drawn-out glass tube pipettes, as is practised by the Pasteur School. This technique is at once simple and invaluable. The preparation of these pipettes will be understood from Fig. 5096.

The glass tubing, which has a diameter of about 8 mm., is cut up into lengths of about twelve inches. By means of the blast lamp a slight constriction is made at about two inches from each end. This serves to prevent the cotton plug from falling down, and also tends to keep the liquid from reaching the cotton. The ends of each tube are then carefully rounded out in the flame. A piece of cotton is then pushed into the end of each tube. The tubes thus prepared (Fig. 5096, *a*) are then sterilized in the dry-heat oven, after which they may be stowed away for future use.

Whenever it is desired to make a pipette, one of these tubes is heated in the middle in a blast flame, and when the glass has thoroughly softened, the two halves are slowly drawn apart. A relatively wide, thick-walled capillary, about sixteen inches long, is thus obtained (Fig. 5096, *b*). This is then sealed in the flame in the middle, and the result is two pipettes. For transferring large quantities of liquid a bulb is blown in the pipette (Fig. 5096, *c*). This is made by directing a narrow blast flame against the tube, which is at the same time rotated. As the glass softens the ends are slightly pushed together, so as to form a thick ring of glass. This is repeated once or twice. Finally a large blast flame is turned on, and when the thickened glass is perfectly soft, the end is brought into the mouth and the bulb is blown. The glass should be rotated during this operation, and in fact in all work of this kind.

To use a pipette, the mouth end should first be rolled for a few seconds in a flame so as to insure sterility; the capillary end is then scratched with a file and the tip is broken off, after which the capillary is flamed. As soon as the tube has cooled, which fact can be ascertained by blowing through the pipette against the back of the hand, it is ready for use. The closure of the pipette

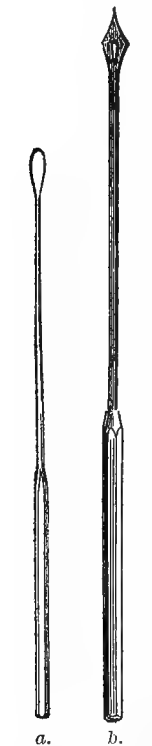


Fig. 5095. — *a*, Roux spatula; *b*, Nuttall's platinum spear.

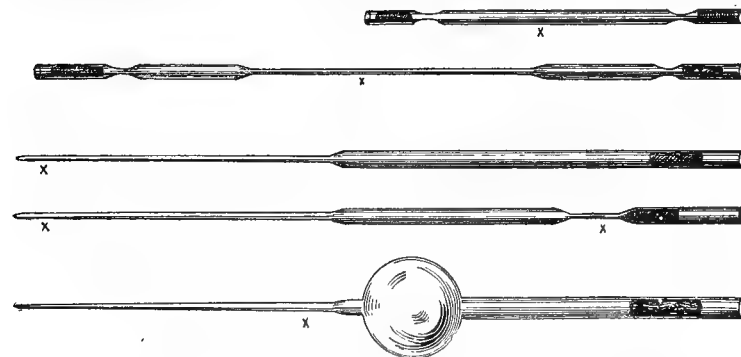


Fig. 5096. — Pasteur Pipettes, showing Method of Preparation. (Novy.)

when it is filled with the liquid is effected by means of the tongue.

The great value of the pipette lies in the fact that it can be made in a few minutes, and can be used to transfer liquids from one tube to another, for drawing blood from the heart, fluids from the cavities, etc. It is indeed even more useful than a platinum wire.

Plate Cultures.—Solid media, such as gelatin or agar, either plain or modified, are employed for this purpose. The starting-point in this method were the slide cultures

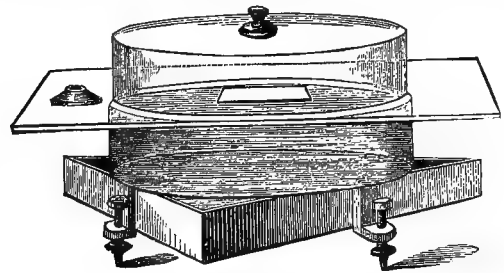


Fig. 5097. — Koch's Levelling Apparatus.

used by Koch in his early investigations. The liquefied gelatin was poured upon the surface of sterile glass slides, which were levelled and kept cool by means of the apparatus shown in Fig. 5097. The lower dish was filled with ice-water and the whole was set true by the aid of a small spirit-level. A series of parallel streaks was then made on the solid gelatin by means of a platinum wire, which was dipped in the material to be planted. A number of slides were thus made, after which they were stacked on glass benches (Fig. 5098), and placed in a moist chamber to develop (Fig. 5099). The first streak, on account of the large number of organisms planted, would probably yield a continuous solid growth. The next streak would have fewer germs, and the succeeding ones still less until eventually only single germs would be deposited, separated by an appre-



Fig. 5098. — Glass Benches and Culture Slides.

ciable distance from the following ones. Wherever a single organism was deposited, as a result of multiplication, a colony would soon make its appearance. (See Plate LXI.)

The slide method was soon improved by substituting larger glass plates (10 × 13 cm.). Instead of making streak dilutions as just given, the gelatin was liquefied, inoculated, and poured out upon the sterile plates, which were cooled on the plating apparatus. This method of

plating may be used when the special Petri dishes, ordinarily employed, are not obtainable. The fact that the method required a lot of apparatus, slides, slide-box, levelling apparatus, ice, moist chamber, etc., as well as the fact that contamination from the air and from the dripping of the superposed plates was unavoidable, led Petri to introduce the modification which has almost entirely supplanted the older method.

Gelatin Petri Plates.—In this method, as in the preceding, the gelatin is first melted by immersion in warm water for a few minutes. By means of a sterile, looped, platinum wire a small quantity of

the material to be examined is transferred to a tube of liquefied gelatin, marked 1. By means of the wire the material is thoroughly mixed with the gelatin. Another tube, marked 2, is then placed beside the first, from which three loopfuls of gelatin are carried over to tube 2, with the contents of which they are well mixed (Fig. 5100). A third tube, marked 3, is then

placed beside number 2, and three loopfuls of gelatin are transferred from tube 2 to tube 3. It is evident from this procedure that even if the first tube received a million germs the second tube would contain only a small fraction, and the third tube would contain still

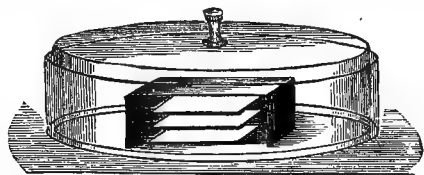


FIG. 5099.—Moist Chamber with Stacked Plates.

less. The platinum wire must of course be sterilized whenever an inoculation is made into a new tube.

A number of Petri dishes (Fig. 5101), which are 10 cm. in diameter and 1 cm. high, are previously sterilized by heating in a dry-heat oven for one hour at 150°, or for a few minutes at 200°, and allowed to cool. To pour the plate, the cotton is removed from one of the tubes, and the open end is rolled for a few seconds in the flame so as to sterilize it. In a few seconds the end of the tube becomes cool, after which the contents are poured out into the Petri dish. The lid of the latter is

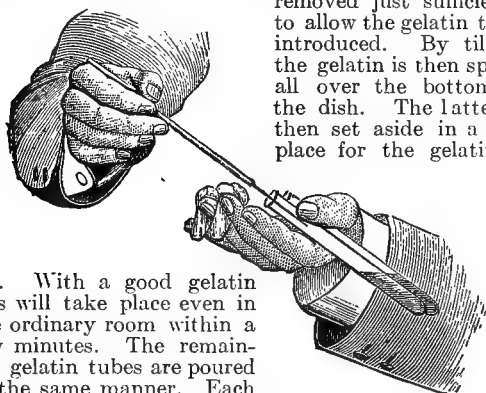


FIG. 5100.—Method of Holding the Tubes when Making Dilutions.

removed just sufficiently to allow the gelatin to be introduced. By tilting, the gelatin is then spread all over the bottom of the dish. The latter is then set aside in a cool place for the gelatin to set. With a good gelatin this will take place even in the ordinary room within a few minutes. The remaining gelatin tubes are poured in the same manner. Each plate should be numbered to correspond to the tube from which it was made. They should be marked also with the date and the kind of material used. A Faber's colored wax pencil is used for this purpose.

Agar Petri Plates.—Inasmuch as gelatin melts at about 25° C. it follows that the method just given cannot be used when the organism requires the temperature of the incubator. In such cases it is necessary to resort to the use of agar. The nutrient again is first melted by heating in a water-bath at 100° C. The flame is then turned out and the tubes are allowed to cool in the water bath until a temperature of about 45° is reached. The agar solidifies at about 40°, and consequently the dilution must be made rapidly and the plates poured before that point is reached. Dilution



FIG. 5101.—Petri Dish for Plating.

cultures are made in the same way as just given for gelatin. The three agar tubes are then poured out into the corresponding sterile Petri dishes. The agar promptly solidifies, and for that reason the spreading

of the agar over the bottom must be hastened. The agar plates are then set aside to develop either at the temperature of the room or at that of the incubator.

Esmarch Roll-tube Culture.—This modification of the plate method does away with the use of any special container other than the test tube. The dilutions in gelatin are made in the usual way. According to the original directions the cotton plug was cut off short, and the end of the tube was covered with a close-fitting rubber cap. The tube was then immersed and rotated in an almost horizontal position in ice-water. The gelatin solidified in an even film over the inside of the test tube (Fig. 5102).

A more convenient way of rolling the tubes was devised by Booker. With the aid of a large test tube filled with warm water a groove is melted into a block of ice. The gelatin tubes are then rolled in this groove until the gelatin solidifies in a smooth, even film. Nuttall has modified this procedure by replacing the ice block with a marble block provided with grooves for the test tubes. Running tap water serves to cool the tubes.

If the tubes are not rolled smoothly they can be softened by gentle warming and rerolled. One advantage of this method lies in the fact that desiccation can be retarded more than with the other methods. Air contamination is likewise diminished. On the other hand, the presence of a few liquefying bacteria may spoil the tube. The Esmarch roll tubes should be kept in a cool place to prevent melting. When the colonies develop they may be examined by placing the tube on the stage of the microscope. To transplant the colonies a platinum wire, provided with a hook, as shown in Fig. 5094, should be used.

Shake Cultures.—Dilutions are made in gelatin or agar as heretofore described. The tubes are then solidified in an upright position and allowed to develop. If it is desired to transplant a given colony the test tube should be scratched with a diamond at about the level of the colony. On touching the scratch with a hot rod the crack can be led around the tube, after which the two parts can be separated. By means of a sterile knife the medium can be cut and the colony exposed. In the case of agar the entire cylinder of agar can be forced out of the tube into a sterile dish by the cautious application of a flame to the lower end of the tube.

The method offers a convenient means of determining whether or not the organism planted generates gas. If such is the case gas bubbles will make their appearance in the medium. As will be seen later this method is also useful in connection with the cultivation of anaerobic bacteria.

Streak Cultures.—This procedure, which is essentially the same as that used by Koch in his slide cultures, is very frequently made use of at the present time. Thus, sterile gelatin or agar may be poured into sterile Petri dishes, and after the material has solidified a series of parallel streaks may be made with an infected wire. The Kruse platinum brush may be used to spread the organisms over the surface. A narrow glass rod, bent and flattened at the end, has been used for spreading

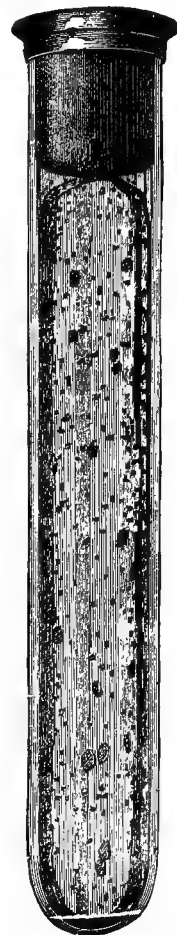


FIG. 5102.—Esmarch's Roll Culture.

gonorrhœal pus over plates. Cotton swabs are used for the same purpose in the case of diphtheria.

As in the case of the Esmarch roll tube, the Petri dish may be omitted in this method. In that event the gelatin or agar is melted and allowed to solidify in an inclined position. The streaks are then made on the surface of the inclined medium. Potato tubes are inoculated in the same way. (See Plates LX. and LXI.)

To obtain perfectly isolated colonies by this method the same wire should be used to make parallel streaks on each of four or five tubes. When the colonies develop, transplantations can be made by means of a bent wire.

Hanging-drop Cultures.—A concave or well slide, shown in Figs. 5117 and 5118, is used. The cover-glass must first be sterilized by passing it several times through a flame. A large drop of sterile bouillon is then placed in the centre, and this is inoculated with the germ to be studied. The slide with a ring of vaseline is then inverted and brought down upon the cover-glass, after which the preparation is turned over. Care must be taken to see that the vaseline closure is perfect. This method of cultivation is used to study the multiplication of the bacteria under the microscope.

Hanging-block Cultures.—In order to be able to study the morphology and the multiplication of the diphtheria bacillus to better advantage than that afforded by the hanging drop, Hill devised the following procedure: Melted nutrient agar is poured into a Petri dish to a depth of about one-eighth to one-quarter inch. When cool, a block of agar is cut out, about one-quarter to one-third inch square, and of the thickness of the agar layer in the dish. The block is placed, under surface down, on a slide and protected from dust. A suspension of the growth to be examined is then made in sterile water or a bouillon culture is used. The suspension is spread over the upper surface of the block as if making an ordinary cover-slip preparation. The slide and block are then set aside in the incubator at 37° for five or ten minutes, to dry slightly. A clean sterile cover-slip is then placed on the inoculated surface of the block in close contact, avoiding large air bubbles. The slide is then removed from the under surface of the block, and the cover slip is inverted so that the agar block is uppermost. With the aid of a platinum wire a drop or two of melted agar is run along each side of the agar block, to fill the angles between the sides of the block and the cover-slip. This seal hardens at once and prevents slipping of the block. The preparation is again placed in the incubator for five or ten minutes to dry the agar seal. Finally the preparation is inverted over a moist chamber or suitable well slide. The cover-slip is sealed in place with white wax or paraffin. Vaseline cannot be used because it softens at 37°. The "hanging block," thus prepared, is examined on a warm stage or in the incubator-room.

Transplantation of Colonies.—The entire object of making plate culture by any one of the several methods given is to obtain single isolated colonies, which can be transplanted to other media, and the organism present can then be studied in perfectly pure condition. The colony as indicated is presumably derived from a single cell, and consequently is a pure culture. The transplantations or subcultures can be made to gelatin, agar, serum, bouillon, milk, etc. When the colonies are on a plate or in a Petri dish a straight wire is used. The plate is first carefully examined under the microscope, and a colony is selected which is clearly single. If possible it should be the only one in the field of the No. 3 or one-third inch objective. The farther apart that the colonies are the less likely are they to intermingle. As originally directed, the colonies were touched under the microscope by a sterile platinum wire, and in this way a few of the bacteria were removed. Care had to be taken that the wire did not touch the objective or any other part of the gelatin. This operation of "fishing," as it is called, obviously requires considerable practice and care. An equally good procedure is to pick out the desired colony under the microscope. The tube of the

microscope is then raised, and the point of the sterile wire is brought down so that it cuts the colony and nothing else. The tube is then again lowered and the site of the colony examined to make sure that nothing but the colony was touched. If such is the case the wire is then used for the subculture.

Stab Cultures.—A tube of solid gelatin is taken, the cotton plug is seized by the right little finger and removed. The mouth of the tube is then flamed, after which the wire, laden with the bacteria, is inserted and carefully passed down the centre of the gelatin. The organisms are thus planted along the line of inoculation. The cotton plug is replaced and the tube is labelled and set aside. The form of the growth is then noted from day to day, also the presence of gas, liquefaction, pigment, etc. The characteristics of the stab cultures are of the very greatest importance in the identification of bacteria. If the gelatin is old and partially dried, the passage of the needle is likely to cause a split in the medium. This can be avoided by melting and resolidifying the gelatin. (See Plates LX. and LXI.)

Streak Cultures.—These are also known as "smear cultures." The gelatin or agar tubes are melted and solidified in an inclined position. Similarly solidified blood serum is also used; so also are the potato tubes. The infected platinum wire is drawn along the middle of the surface of the medium by making one single streak. The growth develops along the line of inoculation, and spreads in a more or less characteristic manner. (See Plates LX. and LXI.)

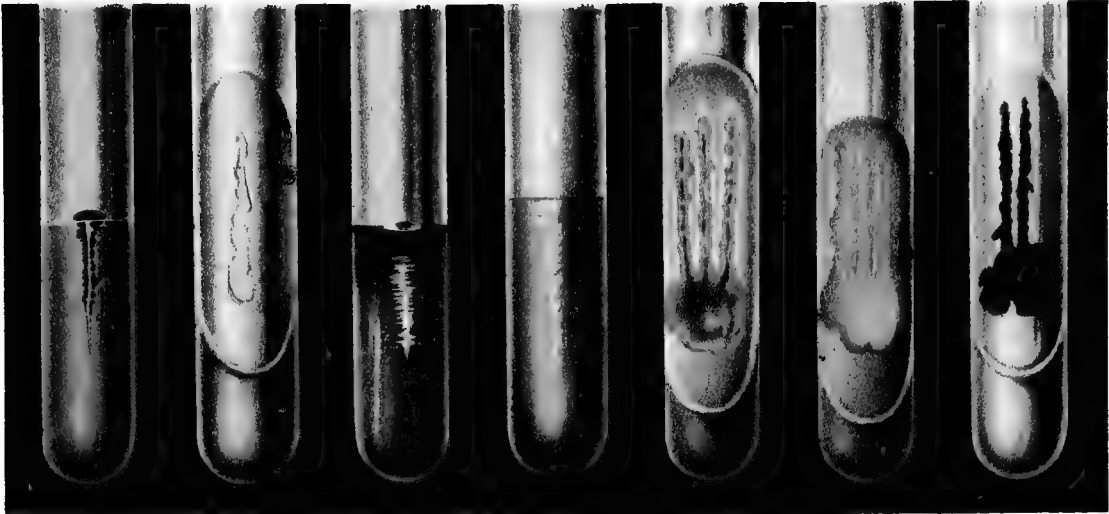
Flask Cultures.—Flat flasks may be used for the cultivation of bacteria *en masse* where the organisms are desired in large quantities. The flask possesses an advantage over the Petri dish in that it is much less likely to become contaminated from without. For this purpose the Kolle culture flask, or any similar flat flask with a smaller mouth, may be employed. To a properly plugged and sterilized flask, sufficient fluid gelatin or agar medium is added to form a layer about a quarter of an inch in thickness over one side. It is again sterilized by steaming and the medium is allowed to solidify with the flask lying on its side. When solid the free surface of the medium may be inoculated with organisms in broth or salt solution suspension by spraying or brushing over with a Kruse's brush. After the growth has sufficiently developed, it is removed by being scraped off. A spatula, glass rod with angle at end, or similar instrument may be used for this purpose. Sterile broth or salt solution may be used to aid in washing the culture free. For the cultivation of bacteria on a large scale, Novy and Vaughan introduced large metallic tanks, with tightly fitting covers.

Liquid Cultures.—The tubes of sterile bouillon, milk, serum, etc., are inoculated by simply introducing some of the material from a colony by means of the sterile wire.

The subcultures from tube to tube are made in the same way as just given. The drawn-out glass-tube pipettes and spatulas can be used to transfer the material from one tube to another or to flasks.

ANAEROBIC CULTIVATION OF BACTERIA. The methods just given are essentially aerobic, since there is free access of air. As is well known there are two classes of bacteria with reference to their oxygen requirements. The aerobic bacteria live in the presence of air, while the anaerobic thrive only in the absence of oxygen. In order to cultivate the latter, special methods must, therefore, be employed which will supply the needed conditions. Numerous procedures have been devised for this purpose, and to give all of these would be beyond the scope of this article. It will be sufficient to indicate the principles which serve as a basis for these methods, and to describe those which are most widely used.

1. *Exclusion of Oxygen.*—This was accomplished by Pasteur in his early work by pouring a layer of oil upon the culture fluid. This served to exclude the air and allowed the bacteria to develop. Koch obtained anaerobic conditions by covering the surface of the gelatin



1.
Black
Yeast.

2.
Red
Yeast.

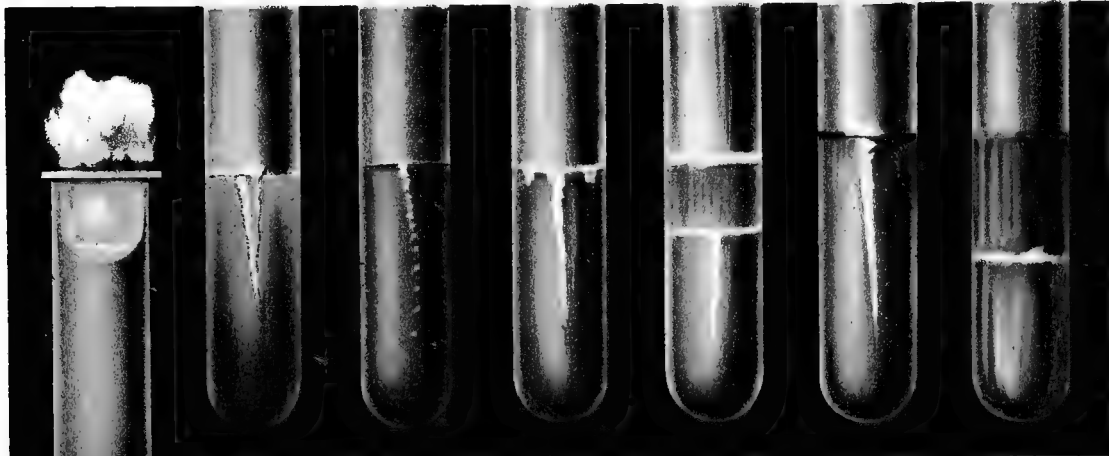
3.
Brown
Yeast.

4.
Yellow
Sarcina.

5.
Bacillus
Prodigiosus.

6.
Bacillus
Indicus.

7.
Bacillus
Violaceus.



8.
Bacillus
Fluorescens.

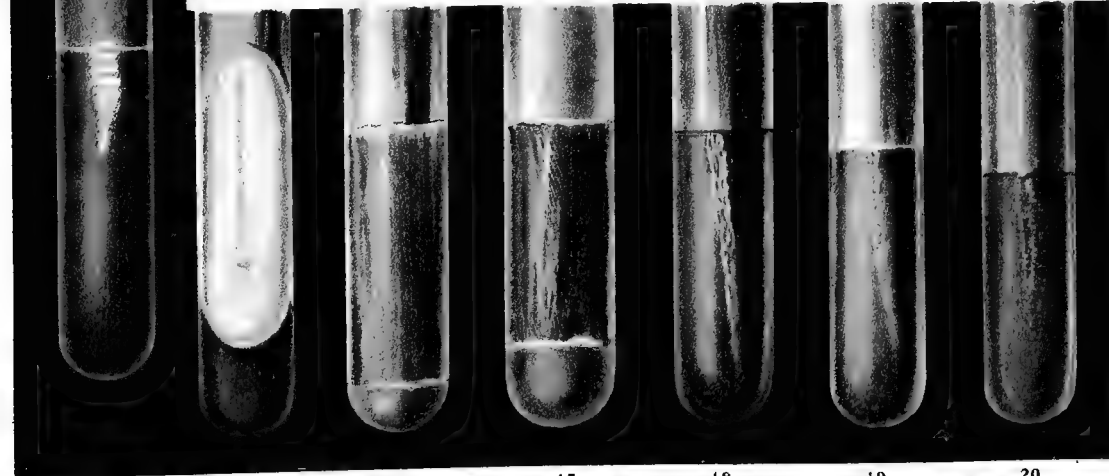
9.
Micrococcus
Lactis.

10.
Bacillus of
Sour Milk.

11.
Bacillus
Butyricus.

12.
Bacillus of
Blue Milk.

13.
Bacillus of
Green Pus.



14.
Micrococcus
Tetragenus.

15.
Staphylococcus
of Osteo-
myelitis.

16.
The same
in gelatine.

17.
Staphylococcus
pyogenes
albus.

18.
Streptococcus
pyogenes.

19.
Streptococcus
of erysipelas.

20.
Streptococcus
of Puerperal
Fever.

TEST-TUBE CULTURES.

Reproduced from Huber & Becker's "Untersuchungs-Methoden."

plates with a thin sheet of mica. Others have done the same with glass plates.

The Liborius method of cultivation in deep layers falls under this head. It is simple and is constantly used. Ordinary stab cultures are made in the suitable media, preferably glucose agar. Another tube of agar is liquefied, cooled to about 50°, and the contents of this are then poured on top of the stab culture. Care must be taken to flame the mouths of both tubes so as to avoid contamination. The upper layer of agar serves to keep out the air. The cultures can be prepared equally well by employing agar or gelatin tubes filled with the medium to a depth of about two inches. It is well to place the tubes in boiling water for some time to drive off the absorbed oxygen, then solidify rapidly by chilling. Use a tightly fitting stopper in the tube to exclude the air. After the stab is made, the line of puncture closes up itself, and the growth then develops in the lower part of the tube, as shown in Fig. 5103.

Isolated colonies can also be obtained by this method. The liquefied medium is inoculated and dilutions are made as for shake cultures. The tubes are then solidified, and if necessary an additional layer of medium is poured on top. When the colonies develop they can be reached according to the directions given under shake cultures. Another procedure is to make Es-march roll tubes and then fill the inside with gelatin or agar.

The drawn-out glass-tube pipettes (Fig. 5096) have been used by Roux for this same purpose. The liquefied medium is inoculated and drawn up into the pipette, which is then sealed above and below the contents. The colonies which develop can be reached by cutting the glass. A somewhat similar procedure was devised by Wright. A short glass tube with constricted ends is used. Each end has a piece of rubber tubing attached. One of these is connected with a glass tube which projects through the cotton plug of the test tube. The test tube contains bouillon, and this contrivance is sterilized and inoculated. The bouillon is then drawn up into the constricted tube, which is sealed by simply pushing down on the tube, so that both rubber ends are bent back on themselves.

2. *Displacement of Air.*—This is accomplished by passing through the tube or a suitable container an inert gas till all the air has been displaced. Hydrogen is the least injurious gas for this purpose. It can be generated from zinc and sulphuric acid in a Kipp's generator. The gas should be washed by passing successively through alkaline lead acetate, six per cent. potassium permanganate, and finally through a solution of silver nitrate.

After passing through the apparatus the gas is sent through a small wash bottle which serves as a valve to prevent air from entering when the current slows up. Such a wash bottle is shown in Fig. 5105, *H*. After the gas has passed for an hour or more it should

be tested by applying a light as it leaves the wash bottle. If the flame burns with explosions it is evident that all the air has not been displaced. The operation is continued until the gas burns evenly at the mouth of the tube. Owing to the danger of explosion the light should never be applied to the outflowing gas without the safeguard of the water valve.

One of the earliest attempts at making tube cultures by this method was that of Liborius. He made use of a special test tube with a delivery tube fused into

the side. After inoculation of the liquid medium, gas was passed through, and finally the neck of the test tube, as well as the end of the delivery tube, was sealed in the flame. This method is of only very limited application, and requires much time and is expensive. Fraenkel's modification is a distinct improvement. Ordinary large test tubes are used. These are provided with rubber stoppers and delivery tubes, as shown in Fig. 5104. After the inoculation of the medium and expulsion of the air, the tubes are sealed in the flame. If it is desired to obtain colonies, the tube can be converted into an Es-march roll tube.

This principle has been adapted in various ways for the purpose of obtaining plate cultures. Kitasato employed a flat bottle, having a tube fused at the lower end. The dilutions were made in the ordinary tubes, after which the material was poured into these flasks, which were connected in series and hydrogen passed through. Finally the ends were sealed by fusing in the flame, while the neck of each flask was closed with a clamped rubber tube. Several modifications of this bottle have been made, but they are little used, since methods were soon perfected whereby it was possible to make Petri plates in hydrogen.

One of the earliest attempts in this direction was that of Blücher, who made use of a funnel which was weighted with lead and inverted over the plates in a larger dish. Air was excluded by means of glycerin water. Hesse inverted a glass vessel in a circular trough filled with mercury. Liborius used a copper bell-jar which was compressed against a rubber gasket by means of set-screws; others made use of bell-jars inverted upon a ground-glass surface. In many respects the Botkin apparatus is useful. It is shown in Fig. 5105. It consists of a metal rack on which are placed the Petri dishes. This is set in a large outer dish which contains about an inch of liquid petroleum. A bell-jar is inverted over the stand. The inflow and outflow tubes are of rubber stiffened by a copper wire on the inside. After the hydrogen has been passed for a sufficient length of time, the tubes are withdrawn and the apparatus is then set aside.

The Novy apparatus shown in Fig. 5106 leaves little to be desired. The hollow stopper has two perforations, one of which is connected with a glass tube which extends almost to the bottom of the bottle. In the case of the plate apparatus the tube may be continued by means of a piece of rubber tubing. A perfect seal is obtained by simply turning the stopper through an angle of 90°.

The bottle (Fig. 5106, *A*) is made in two sizes, 8 × 16 and 10 × 20 cm., which dimensions do not include the neck. A piece of cotton should be placed on the bottom.

The ordinary test tubes containing any medium are inoculated in the usual way. The cotton plug is then cut off square, and by means of a pair of crucible tongs the tube is lowered into the bottle. It is advisable, if the cotton plug is very tight, to loosen it up by partially pulling it out. A single jar can be filled in this way

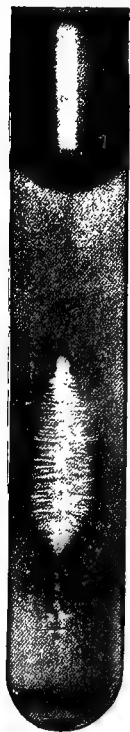


FIG. 5103.—Liborius Deep Stab Culture showing Growth of the Tetanus Bacillus.

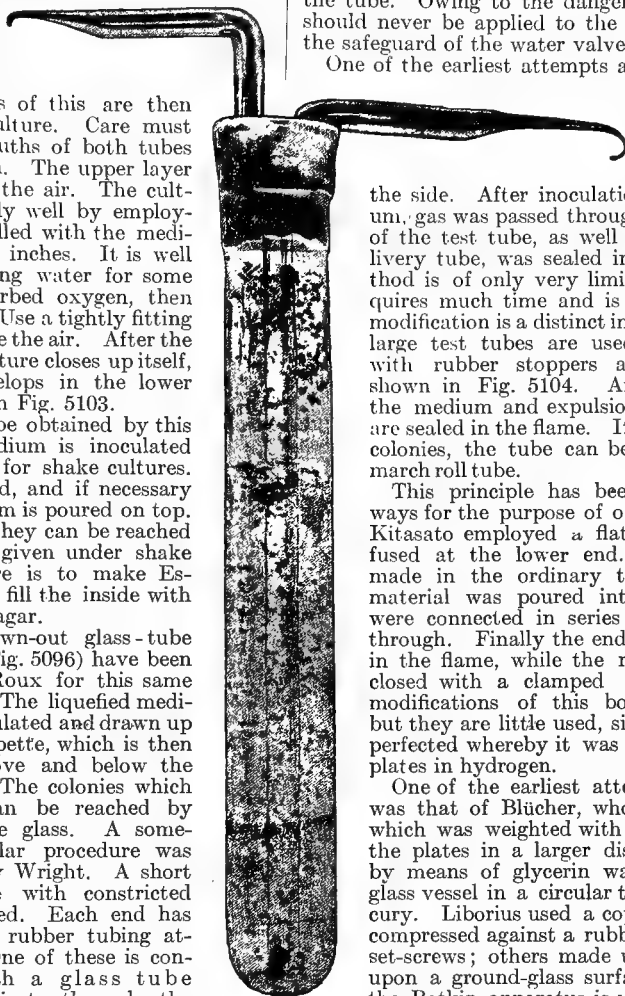


FIG. 5104.—Fraenkel's Modification of Liborius Tube for Anaerobes.

with a large number of tubes containing either solid or liquid media. The stopper is then put in place and the apparatus connected with a hydrogen generator. When the gas has passed for a sufficient length of time the

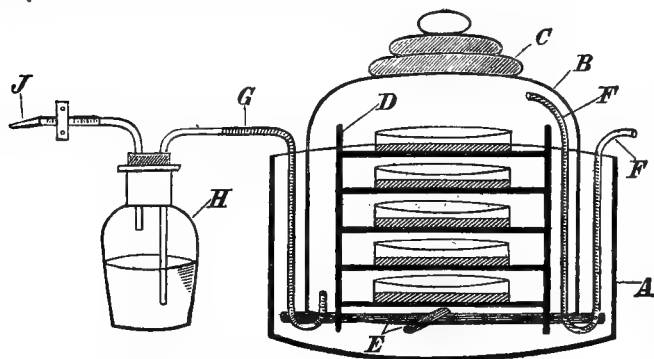


FIG. 5105.—Botkin's Apparatus for Plate Culture of Anaerobes.

bottle is closed by giving the stopper a turn. As will be seen, this jar can be used likewise for the pyrogallate method.

The plate apparatus shown in Fig. 5106, *B*, consists of two parts. The inner dimensions of the lower part are 12×12 cm. The Petri plates are stacked into this compartment. The flanges are covered with a mixture of beeswax and olive oil (1:4). The two parts are then brought together and a rubber band is slipped over the outer edge of the flanges. Two or three clamps or small vises are now applied. The jaws of these should be covered with a piece of rubber tubing. Gas is passed as in case of the bottle, and at the conclusion of this operation the stopcock is given a turn so as to seal the apparatus.

The other modification (Fig. 5106, *C*) has a special stopper, which enables it to be used for vacuum cultures. It can, however, be employed equally well for hydrogen cultivation. Moreover, both forms of the plate apparatus, as well as the bottle, can be used for the pyrogallate method.

3. *Absorption of Oxygen*.—The most convenient absorbent for this purpose is an alkaline solution of pyro-

gallic acid and a suitable support. The tube containing the nutrient medium is inoculated in the usual way and placed on this support. Finally 10 c.c. of a ten-per-cent. solution of potassium or sodium hydrate is added from a pipette, as rapidly as possible, and the tube is then quickly closed with the stopper.

As mentioned above, the Novy apparatus can be employed for the pyrogallate method. In the case of the jar a wide tube is introduced which contains about 2 gm. of the acid. After the culture tubes have all been inserted, about 20 c.c. of a twenty-five-per-cent. solution of sodium hydrate is introduced into the pyrogallate tube from a pipette, and the stopcock is then inserted as quickly as possible and turned. In the case of the plate apparatus a crystallizing-dish, about 10 cm. in diameter and about 2 cm. high, is placed on the bottom, and about 4 gm. of pyrogalllic acid added. A couple of strips of glass are then placed on top, and on these are stacked the Petri dishes. Twenty-five cubic centimetres of the strong alkali is introduced in the manner just mentioned, after which the top is put into place, the clamps and the rubber band are applied.

Wright's method will be found to be very useful for occasional cultures. The cotton plug is cut off square and pushed down about 1 cm. into the tube. The plug is made of absorbent cotton. It is then moistened with about 4 c.c. of a strong solution of pyrogalllic acid, after which about the same volume of strong sodium hydrate (1:2) is added. The tube is closed as rapidly as possible with a tight-fitting rubber stopper. Obviously, solid pyrogalllic acid may be used.

It will be seen that the pyrogalllic-acid method is extremely convenient and very simple, requiring a minimum of time and expense. The method is also applicable for the *hanging-drop examination* of anaerobic bacteria. A drop of alkali and of the acid can be placed on the side of the concave slide. After the cover is in place the slide can be tilted so as to bring the two liquids together. A special slide for this purpose was devised by Braatz (Fig. 5108).

The hanging drop is made and placed over the well. The flat flask contains the pyrogalllic acid and communicates with the space below the drop. Strong al-

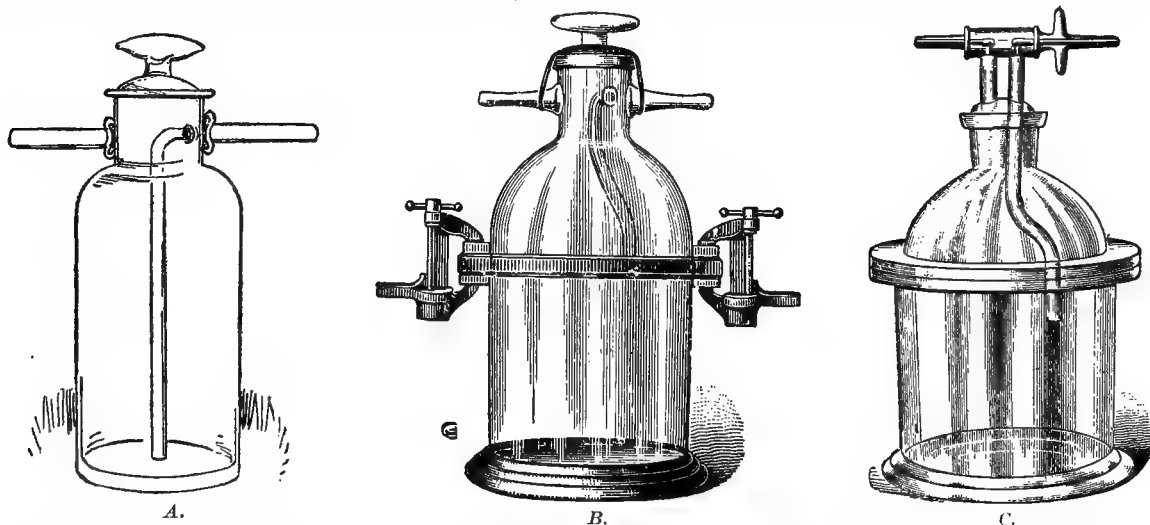
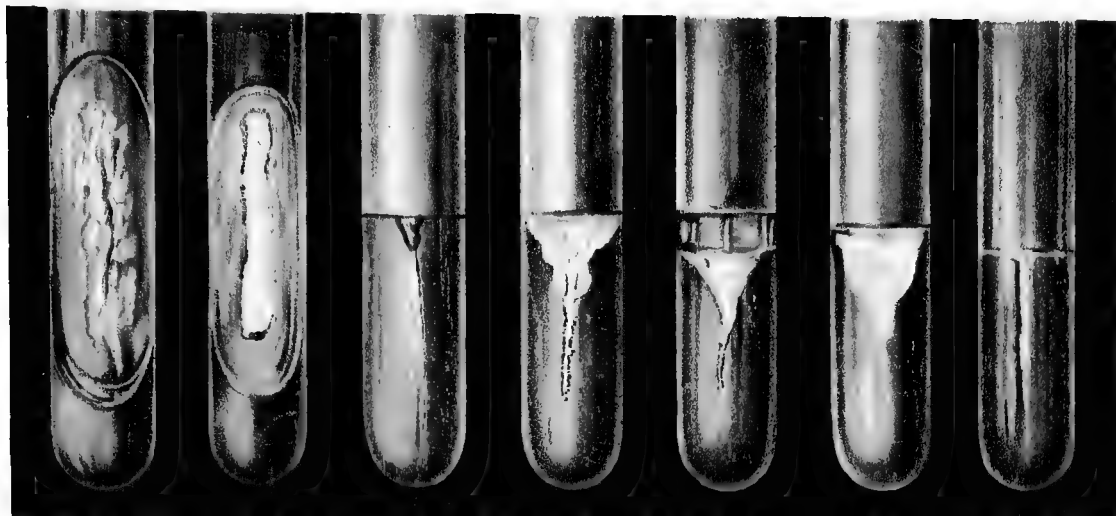


FIG. 5106.—Novy Apparatus for Anaerobes. *A*, Bottle for tube cultures; *B*, jar for Petri plates; *C*, jar for plates with special stopcock for vacuum culture.

gallic acid. The principle was first utilized by Buchner for tube cultures, as shown in Fig. 5107. The large outer tube is provided with a closely fitting rubber stopper. On the bottom of the tube is placed about a

kali is finally added and the flask is closed with a stopper. Pyrogalllic acid can also be employed in connection with Hill's "hanging-block" culture. Another apparatus for anaerobic hanging drops is that of Kühne.



1.
Bacillus of
Tuberculosis.

2.
Bacillus of
Cholera Asiatica.

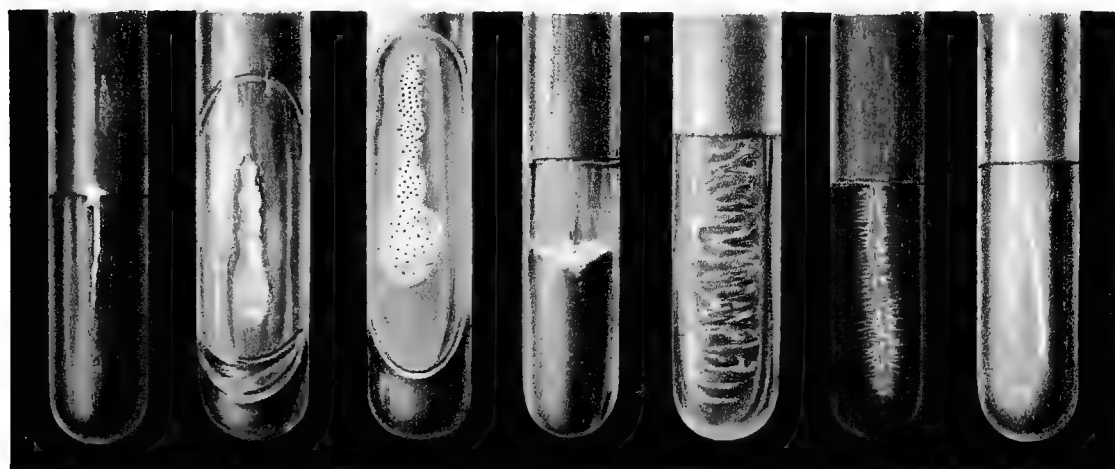
3.
The same
in gelatine.

4.
Finkler-Prior's
Comma Bacillus.

5.
Denecke's
Bacillus

6.
Miller's
Bacillus.

7.
Bacillus of
Typhoid Fever.



8.
Pneumococcus.

9.
Bacillus of
Glanders.

10.
Bacillus of
Anthrax.

11.
The same
in gelatine.

12.
Bacillus of
Malignant
Oedema

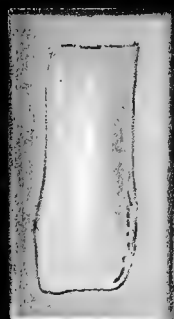
13.
Bacillus of
Septicaemia
of Mice.

14.
Bacillus of
Septicaemia
of Rabbits.

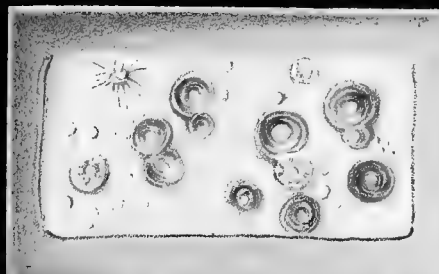


15.
Bacillus of
Chicken
Cholera.

16.
Bacillus of
Pigeon
Diphtheria.



17.
Slide Culture
(reduced)



18.
Plate Culture.
(reduced.)

TEST-TUBE CULTURES.

Reproduced from Huber & Becker's "Untersuchungs-Methoden."

It is very serviceable and can be used for either the gas or pyrogallate process.

4. *Exhaustion of Air*.—Pasteur employed U-shaped tubes, from which the air was removed by means of an air pump. Gruber applied the principle to the tube culture. He used a stout glass tube, which was provided with a stopper, through which passed a short glass tube by which connection was made with the air pump. The test tube was constricted just below the stopper so as to facilitate the subsequent sealing process. The tube was filled in the usual way with the nutrient medium and inoculated. It was then connected with the pump, and as soon as the air was exhausted the tube was sealed at the constriction. The plate apparatus shown in Fig. 5106, C, is intended for vacuum as well as gas or pyrogallate cultures. It can be used for tube or plate cultures.

5. *Mixed Cultures*.—This method of cultivating anaërobic bacteria corresponds to the way in which these organisms grow in nature. If the anaërobic is planted together with an aërobic, the latter will consume all the oxygen in the immediate neighborhood, and as a result the anaërobe will grow. Thus, if the tetanus and hay bacilli are planted at the same time into a tube of bouillon, they will both develop. Other aërobic bacteria, such as *Bacillus prodigiosus* and *Proteus vulgaris*, can be used for the same purpose. The mixed culture method is also applicable to the cultivation of certain protozoa (amoebæ). But perhaps this is due to altered medium rather than any oxygen requirement. Musgrave and Clegg found that amoebæ could be cultivated upon a special medium when grown with pure cultures of certain intestinal organisms, as *B. coli*.

6. *Cultivation in Air*.—This of course is apparent rather than real. If a tube of glucose gelatin, preferably colored with litmus, be inoculated with an anaërobe and then set aside in the incubator, an abundant growth will develop (Novy's method). Similarly, when deep stab cultures are made of the anaërobes,

it will be found quite frequently that the water of condensation on the top of the medium is cloudy from the growth of the germs. The explanation in the one case is that air is excluded partly by the viscosity of the liquid and partly by the evolved gases. The gas formation accounts for the growth of the germs in the water of condensation. The culture in glucose litmus gelatin is by far the simplest way of growing anaërobes. Moreover, the cultures thus obtained retain their vitality for many years. In some cases the author has recovered cultures from tubes five and six years old.

Collodium Sacs.—This method of cultivating has been used extensively by the Pasteur School for exalting the virulence of bacteria. The underlying idea is to grow the organisms in the peritoneal cavity of an animal, and under such conditions that the waste products of the germs will be removed, an abundant supply of nutrient material furnished, and the germs themselves protected against the action of phagocytes. This is accomplished by enclosing the bacteria in a hermetically sealed sac, the walls of which are permeable to the waste products of the germs and to the soluble proteids of the peritoneal fluid. Several Russian workers have employed for this purpose the inner lining membrane of reeds, but the best procedure is to make the sacs of collodium. Various methods have been devised for the rolling of the sac, but

undoubtedly the best and simplest is that preferred in the author's laboratory by Gorsline.

The rolling tube employed for making sacs is about twelve to fifteen inches long, and of any width that may be desired. For ordinary purposes a width of half an inch is sufficient. One end of this tube is rounded off like a test tube, and has a 2-mm. opening at the tip. This opening is first closed with collodium either by touching it with the cork which has been covered with the solution, or the collodium may be applied with the finger. Care must be taken to see to it that the collodium does not get inside of the tube. In a few seconds the layer is dry enough to go ahead.

The collodium used is the United States Pharmacopœia solution, which by exposure to the air has been concentrated by one-third or one-half. It should be perfectly clear, and if not it must be filtered through cotton by the aid of a pump. The collodium can be kept in a glass-stoppered cylindrical vessel, such as is used for the collection of blood. The collodium is inclined till it comes within a few inches of the opening.

The rolling tube, with the opening freshly closed, is dipped in the collodium and rolled several times in the liquid. It may be rolled so that only the lower side of the tube touches the collodium. If the sac is to be very thin it is sufficient to roll the tube but two or three times, after which it is raised from the liquid and rolled in the ether atmosphere in a horizontal position till the collodium has set. If the layer is not thick enough the tube can be returned to the collodium, but care must be taken to avoid the formation of air bubbles. The coated tube is finally rolled in the air until it has reached the proper consistence. This can be ascertained by touching the thickest part with the finger. The collodium layer should be rather firm. The tube is then immersed in distilled water for a minute or two. If the collodium is not sufficiently hard, it will cloud or become milky on contact with the water. It should remain perfectly clear, and when finished a thin sac placed in water is almost invisible.

To detach the sac the tube is filled with distilled water, and by blowing into the open end the water can be forced through the opening below and upward between the sac and the tube. By slight manipulation with the fingers the detachment can be effected readily on all sides. The free end is then trimmed square, after which the sac is placed in distilled water, where it remains until it is ready to be attached to the glass tube.

An ordinary test tube having a diameter slightly less than the sac is constricted in the blast flame at about two inches from the end. A scratch is then made, about a half an inch below the constriction, with a diamond, and with the aid of a hot rod the end is removed. The resulting tube has the form shown in Fig. 5109, a. The cut end should be rounded in the flame so as to remove the sharp edge.

The inside of the neck of the sac is dried by means of filter paper, after which the end of the tube is inserted.

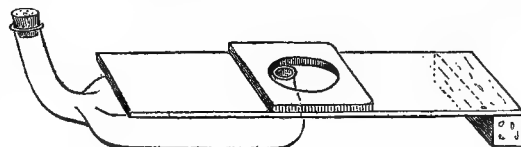


FIG. 5108.—Braatz's Slide for Anaerobic Hanging-drop Examinations.

This can be done more easily if the end of the tube is previously dipped in alcohol. The next step, that of shrinking the sac upon the tube, is very important and requires care. Most of the shrinking is done by rotating the tube, in a horizontal position, some distance above a small spare-flame burner. In this way the collodium can be made to contract down upon the glass, but the operation must be done slowly and at some distance above the flame, otherwise there is danger of ig-

ning the sac. The adhesion is rendered more complete by the application of a hot glass rod. Finally a silk thread is wound as closely as possible over the glass neck, and this in turn is covered with a layer of collodium. The sac now has the appearance shown in Fig. 5019, *b*. The finished sac is now filled with distilled water and placed in a test tube on foot, which also contains water (Fig. 5109, *c*), and the whole is sterilized by steaming in an autoclave for half an hour at 110°.

When the sac is to be used, the water is removed from the inside by means of a drawn-out pipette and refilled in like manner with bouillon which has been inoculated

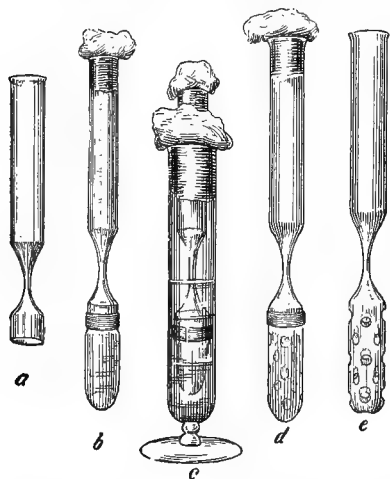


FIG. 5109.—Preparation of Collodium Sacs. (Novy.)

with the organism to be tested. The threaded part is then wrapped in a piece of sterile filter paper, for convenience in handling, and the constriction is sealed in a sharp-pointed flame. The sealed sac is then placed in a sterile test glass.

The rabbit or guinea-pig which is to receive the sac is now attached to a holder and the hair is removed from the abdomen. The field of the operation is thoroughly washed with lysol or mercuric chloride. After the animal is anesthetized an incision is made in the abdominal wall, and through this the sac is introduced into the peritoneal cavity. The incision is then sewed up and covered with cotton and a little collodium.

The sac is allowed to remain in the animal for a few days or even for several months. To remove it the animal is killed with gas. The sac is freed from the adhesions and transferred to a sterile test glass with the glass end downward. By means of a hot rod an opening is burned into the end of the sac, and through this the contents are removed by means of a drawn-out tube pipette. When large sacs are to be inserted into an animal it is advisable to strengthen them by placing within a perforated glass tube as shown in Fig. 5109, *d*, *e*.

The collodium sacs can be used not only as just described, but also with marked advantage for dialyzing experiments. For this purpose the sacs can be made an inch or more in diameter and twelve or fifteen inches long. The thin collodium membrane is considerably more permeable than parchment paper.

Mechanical Separation of Bacteria from Fluids.—For this purpose various types of the centrifuge are used. It is essential that they run smoothly, and revolve at a high speed. The type best adapted for the separation of bacterial and other cells from fluids, pathological exudates, etc., are those equipped with slender glass tubes with conical ends to collect the sedimenting material. They are usually driven by means of water or electric motors. The electric-motor type is more satisfactory and may be procured to be driven by cells, storage battery, direct or alternating current. The ordi-

nary clinical centrifuge driven by hand may be used, but in most cases this is exceedingly slow in sedimenting organisms.

Drying of Bacteria, Toxins, Antitoxins, etc.—In the chemical or biological study of bacteria and their products, it frequently becomes necessary to remove the water content. Since the labile constituents would be destroyed if dried by heat, as in ordinary chemical manipulations, other means must be used. This can best be done by drying *in vacuo* in the presence of certain substances, as phosphoric anhydride (P_2O_5) or concentrated sulphuric acid (H_2SO_4) which readily absorbs the water vapor. The temperature may be kept at that of the working-room or even lower. Most suitable for this purpose is the ordinary heavy glass vacuum desiccator. This is partially divided, with an upper and lower chamber, by means of a movable perforated porcelain plate which forms a shelf for receptacles. Either in the wall or cover of the desiccator a heavy glass tube with cock is fused or passed by means of a ground-glass stopper. This forms a means of communication with the interior of the vessel. The apparatus must be of heavy construction to prevent breakage from the external air pressure when air content is exhausted. For use, first place in the bottom chamber a layer of concentrated sulphuric acid, or, better, phosphoric anhydride, filling the chamber about one-quarter to one-half full. The material for drying has been previously spread or poured in a flat dish, such as the halves of a Petri dish. It is now placed on the porcelain shelf over the water-absorbing substance. The cover is adjusted and firmly sealed in position with an adhesive paste. It is well also to use the same paste on the glass stopcock to prevent leakage at that point. Such a paste may be prepared by taking one part of pure rubber (black elastic rubber tubing cut in small pieces), one part of paraffin, and three parts of vaseline. Mix together and heat until dissolved. Take extra thick-walled rubber tubing and connect an air pump (of the large type) to the exhaustion tube of the desiccator. Open the glass stopcock and pump out the air to produce vacuum. At once close the glass stopcock of desiccator tube, and observe if any air leaks are evident. If not, detach pump. It is necessary to pump out the desiccator at least once a day until the substance is entirely dry. The ordinary water pump cannot be used owing to the water vapor which is always present and travels back during exhaustion.

INOCULATION OF ANIMALS.—According to the nature of the experiment these are made with pure or impure cultures of bacteria, or with the chemical products elaborated by them. The use of impure material is met with in diagnostic work. Thus in suspected glanders the discharge is introduced into animals in order to ascertain if the bacillus of glanders is present. The same is often done in tuberculosis, pneumonia, bubonic plague, anthrax, tetanus, rabies, etc. In all these experiments the animal serves as a plate, since it eliminates all the saprophytic bacteria which may be present in the original material and allows the disease-producing ones to develop in pure or almost pure cultures. The inoculation with pure cultures is made to test their identity, to study their effect upon animals, to ascertain the diverse means of infection, and for purposes of immunization. The inoculation with the chemical products enables one to ascertain the presence of poisonous substances, or to produce vaccines or antitoxins.

The inoculations may be made with a fine needle or lance, but more often with the aid of a syringe. The drawn-out glass-tube pipette is also used as a means of introducing infectious material.

The syringe used varies with different workers. The Germans are especially favorable to the Koch syringe, which consists of a glass cylinder, graduated, the narrow end of which connects with the needle while the upper end fits into the metal collar of a rubber bulb. The advantage claimed is that the cylinder and needle can be effectively sterilized by dry heat. As a matter

of fact the Koch syringe is extremely inconvenient and unsatisfactory, and equally good results with less time and annoyance are obtainable with the ordinary hypodermic. The latter of course must be sterilized by boiling in water for ten or fifteen minutes. A convenient holder for the syringe is shown in Fig. 5110. When large quantities of liquids are

30 cm. high, 38 cm. deep, and 54 cm. wide. The feet are 12 cm. high.

1. *Cutaneous Application*.—Ordinarily bacteria do not penetrate the unbroken skin or mucous membrane. The direct application of some organisms, even in the absence of any known lesion, leads to infection. This is the case when the virus of the foot-and-mouth disease or the bacillus of plague is brought into contact with the mucous membrane. The pus germs, when rubbed into the skin by the aid of vaseline, may cause infection.

2. *Subcutaneous Application*.—For this purpose the hair is removed from the region where the inoculation is to be made. The place is then rubbed with a disinfectant. In the rat this is usually on the back, at the root of the tail; in the guinea-pig it is on the side. A nick is made with sterile scissors, and then with a narrow scalpel or spatula a pocket is made under the skin. A piece of tissue, a bit of earth, blood-laden wire, etc., is then introduced into the opening, which if made small requires no special closure.

3. *Subcutaneous Injection*.—The suspended material is introduced under the skin by means of a syringe. The

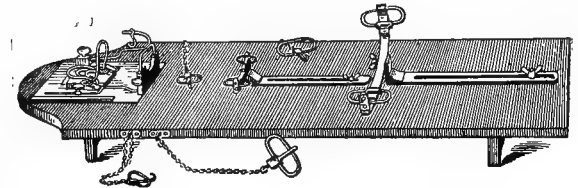


FIG. 5112.—Latapie's Animal Holder. (Novy.)

hair should first be clipped close and the place of inoculation touched up with a disinfectant.

4. *Intravenous Injection*.—In the case of the rabbit this is easily done. The marginal branch of the posterior auricular vein is selected, although it may appear to be narrower than the needle. The hair may be removed and the surface of the ear rubbed freely to stimulate circulation. A clamp is then applied at the base of the ear so as to distend the vein. The needle is then inserted at a very slight angle to the vein. In other animals the jugular can be exposed and the injection made without any difficulty.

5. *Intraperitoneal Injection*.—This procedure is very commonly resorted to. The skin over the abdomen should be raised and the needle of the syringe is then introduced into the cavity. Care should be exercised in order not to penetrate the hollow viscera in small animals. In such case the fluid may enter the intestine, for example, and be discharged without producing any effect. In the case of the horse, while the animal is standing a trocar is introduced through the skin at a point a few inches anterior to the crest of the ilium.

6. *Intrapleural Injection*.—The needle is introduced into the right pleural cavity, care being taken to pre-

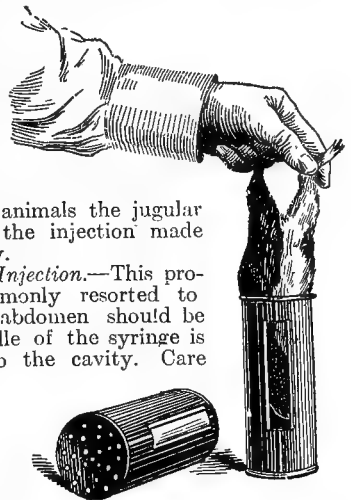


FIG. 5113.—Voges' Holder for Small Animals. (Novy.)

to be introduced, as when injecting horses with diphtheria toxin in the preparation of antitoxin, an apparatus similar to that shown in Fig. 5111 can be used.

The necessary instruments, such as knives, scissors, needles, etc., are sterilized by boiling in water, or better in a saturated solution of borax. A very convenient sterilizer for this purpose is that shown in Fig. 5116.

In all operations the animal must be secured in some way or another. Various kinds of holders have been constructed for this purpose. That of Latapie, shown in Fig. 5112, is very convenient, and is to be preferred to the ordinary models. It can be used for guinea-pigs, rabbits, birds, etc.

The Voges holder, shown in Fig. 5113, is useful for taking temperatures and for injecting small animals. A good substitute can be made by using a glass cylinder. Special holders have been devised for rats and mice. These, however, can be handled best by means of a pair of compression or artery forceps. The animal is seized by the nape of the neck with the forceps, which is then transferred to the left hand. The tail and the hind legs are also held by this hand. The animal in this way is put upon the stretch, and the inoculation can then be made with the right hand. Even full-grown wild rats can be handled in this way without the help of an assistant.

After inoculation the animals are placed in special jars or cages. The ordinary glass battery jars, provided with a galvanized-wire top, weighted with lead, serve to confine rats and mice, and can even be used for guinea-pigs (Fig. 5114). If the animals are inoculated with a very dangerous organism, such as the pest bacillus, it is advisable to place the jar inside of a ten-gallon crock. In special cases, as in animals infected with trypanosomes, bubonic plague, etc., it is well to cover the

cage with a piece of mosquito netting as a safeguard against insects spreading the infection.

Guinea-pigs, rabbits, and the like can be kept in the Vaughan cage shown in Fig. 5115. The cage proper is

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vent any injury to the lung or to the heart. Large amounts of liquid cannot be tolerated by the animal.

7. *Intracranial Injection.*—This method was introduced by Pasteur as a means of surely infecting animals with rabies. The procedure is followed out when inoculating animals either for diagnosis or for the purpose of preparing the vaccine for hydrophobia. It is usually practised on rabbits and guinea-pigs. The skin from between the ears forward is shaven clean and disinfected. An incision about an inch long is then made. The Pasteur School apply a hand trephine, and make an opening into the skull. A small trephine, operated by a dental engine, is much more convenient. In the absence of either an opening may be made into the skull with a stout scalpel. By means of a hypodermic syringe a few drops of the brain or cord suspension are

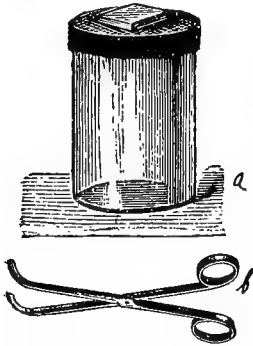


FIG. 5114.—Rat Cage and Forceps. (Novy.)

then introduced under the dura. At times the injection is made into the brain proper, in which case it is spoken of as *intracerebral*. After the injection a suture or two is applied, and the wound is covered with collodium and cotton.

8. *Intra-ocular Injection.*—Cocaine is first applied to the eye, after which this is fixed with forceps and the material injected into the anterior chamber. If desired, an opening can be made with a cataract knife or narrow scalpel and the solid material can be introduced in this way.

9. *Injection into the Lymphatics.*—This is usually made by introducing the material into the testicles.

10. *Respiratory Infection.*—While the preceding methods may be looked upon as wound inoculations, this concerns itself as nearly as possible with duplicating the natural infections along the respiratory tract. The direct method consists in causing the animal to inhale the finely divided material, which can be readily done by means of an atomizer. In some cases the animal is caused to inhale irritating fumes, such as bromine vapor. This excites a slight inflammatory reaction of the respi-

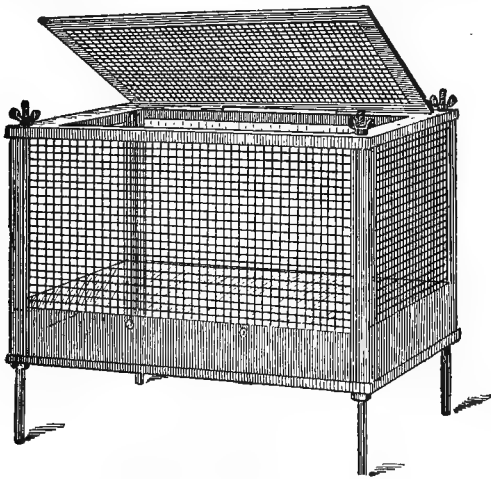


FIG. 5115.—Vaughan Cage. (Novy.)

ratory mucosa, and causes the animal to become more liable to infection.

When the atomizer is used to produce a spray, the operator must take special precaution to protect himself against infection. The animal should be placed in

a specially constructed tight box. All openings for air should be packed with absorbent cotton to act as air filters. The spray can be thrown in through an opening admitting the tube of the atomizer with sufficient cotton wool about it to prevent escape of spray from the aperture. Another procedure may be called the *intratracheal* injection. This is carried out by making an opening into the trachea, and through this introducing the infectious agent.

11. *Alimentary Infection.*—Since water and food serve to introduce the pathogenic agent of many diseases into man and animals, it is necessary at times to resort to a similar method of infection. The animal may receive the infectious agent in water, milk, or in solid food. Thus bread may be soaked in a bouillon culture of the organism. At other times it may be necessary to introduce the material into the stomach by means of a rubber tube. In order to prevent the animal from biting the tube, it is well to pass it through a perforated cork or plug of soft wood. Under exceptional conditions a laparotomy may be made and the material injected into the intestines. This is spoken of as the *intraduodenal* injection.

Observation and Autopsy of Infected Animals.—The matter of suitable caging of animals has already been touched upon. Attention may be called to the need of daily observations of the infected animals, so as to note

the symptoms manifested. The animals must have plenty of food and drink, and must be kept in as clean a condition as possible. Their weight and temperature should be taken daily, for in this way the best information can be gained as to the physical condition of the animals.

When the animal dies it should be autopsied at once, or else

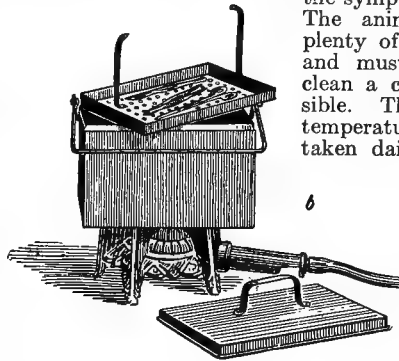


FIG. 5116.—Instrument Sterilizer. (Novy.)

it must be put aside in an ice-box. The need of immediate examination is shown in some of the trypanosomatic infections, as nagana and caderas, where the organisms may disappear from the blood within an hour or so after death. Moreover, delayed examination may lead to the invasion of the organs of the cadaver by the intestinal bacteria, in which case the search for the specific germ is rendered more difficult, if not impossible.

The animal is prepared for autopsy by being placed on its back and tacked down on a board. A convenient board of this kind is one which is about 34 by 54 cm. and has a raised border. The cracks, if any, should be filled with paraffin.

After the animal is laid out, the hair should be thoroughly moistened with mercuric-chloride solution. The necessary instruments can be sterilized in a copper sterilizer, such as is shown in Fig. 5116. In the absence of such an arrangement the instruments may be sterilized by heating directly in the flame, but this, of course, injures them. A searing iron, several drawn-out pipettes and sterile dishes, as well as the necessary media, should be conveniently on hand.

With a sterile scalpel an incision is made along the entire length of the body from the neck to the pubis. Lateral incisions are then made in the direction of each of the extremities, and the two large flaps thus resulting are turned back. The condition of the subcutaneous tissue, the presence of cedema, bloody effusions, enlarged lymphatic glands, etc., are noted. The glands or portions of the tissues may be transferred by means of sterile instruments to a sterile dish. Cover-glass smears or

streaks can be made and examined either at once or later.

The abdominal and thoracic cavities are usually opened at the same time. The abdominal wall in the lower part of the body is slightly raised and nicked with sterile scissors; then the lower blade is inserted and the incision prolonged upward to the diaphragm. The ribs are then cut as low down as possible, and the wedge-shaped piece of the wall of the thorax is removed. The condition of both cavities and of the organs is carefully noted.

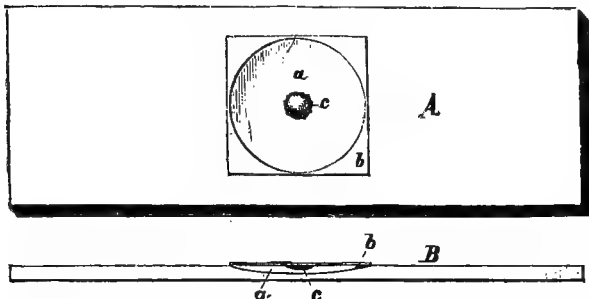


FIG. 5117.—Concave Slide showing Hanging Drop. *A*, Surface view; *B*, side view.

Cover-glass streaks are made from the peritoneal surfaces and from the cut surfaces of the organs, and examined either at once or later. Any fluid which is present in the cavities may be transferred to sterile tubes by means of the pipette.

Cultures should always be made from an intact organ. For this purpose it is cut open with sterile scissors, and a piece of the pulp removed on a sterile wire or by the aid of a Nuttall spear or spatula (Fig. 5095). The heart blood is usually given preference for culture purposes. The pericardium should be opened, after which the surface of the heart is seared with a hot iron. An incision is then made into the ventricle, from which the blood can be removed by the aid of a looped wire. The best way of removing the heart blood is by means of a sterile Pasteur bulb pipette. The end of this is broken, flamed, and when cool it is inserted into the heart, and by suction the blood is drawn up into the pipette. The contents of the tube can then be used to inoculate culture media or for making blood streaks.

After the autopsy the animal should be placed in a vessel and steamed or autoclaved, and eventually burned. The board should be washed with mercuric chloride, and all instruments and utensils should be sterilized by steaming. Throughout the autopsy care must be taken to prevent infection either by the scattering of material on the floor or by its being carried away by insects.

EXAMINATION OF BACTERIA.—In order to gain some definite information regarding the bacteria which develop on the nutrient media or in the animal body, recourse must be had to the microscope. The organisms may be examined in the living condition or in stained preparations. The former procedure is resorted to so as to learn all that is possible regarding the living cell: its form, size, color, granulations if any, motion, grouping of the cells, presence of spores, etc. Such facts are ascertained by making a preparation in which the bacteria will continue to live for some time.

Living Bacteria.—1. The simplest procedure is to place a drop of the bacterial liquid on a slide, after which the cover-glass can be applied and the preparation examined under the microscope. This method is useful for rapid orientation, but it has certain drawbacks, chief among which is the fact that evaporation takes place along the edge of the glass, and as a result currents are established in the liquid. Such currents tend to interfere with the observation of any one organism or group of cells. Again, a preparation of this kind cannot be kept under observation for any length of time on account of the desiccation which soon takes place.

2. The examination in a hanging drop, as it is called, obviates the difficulties mentioned. A rather thick slide with a concave well is used (Fig. 5117). A ring of vaseline is spread around the edge of this well. A clean cover-glass, about three-fourths of an inch in diameter, is placed on the table, and a drop of water is applied to the middle by means of a looped platinum wire. It is desirable that the drop should spread out flat, and if it does not it is because the cover-glass is not clean. The drop of water is then inoculated with a little of the culture. Just enough material is added so that the liquid is slightly cloudy. The vaseline-ringed slide is then inverted and brought down upon the cover-glass. The preparation is turned over, and, if need be, pressure applied to the border of the glass so as to have an airtight hanging drop. Under these conditions evaporation does not take place, and consequently the specimen may be examined for hours, if necessary, without any interference by currents due to evaporation. As mentioned above, this method can be used for the cultivation of bacteria, and thus their growth and multiplication can be followed out. In that case it is necessary to use a flamed cover-glass and a sterile liquid.

Instead of the concave slide a so-called well slide can be used (Fig. 5118). This is essentially a square bit of glass with a circular opening, which is cemented to an ordinary glass slide, and the hanging drop is then made in the manner described.

One disadvantage in either method lies in the fact that the drop is more or less convex, and consequently when using higher powers it is difficult to examine the deeper portions. This difficulty can be overcome by employing the Ranvier slide, which has a circular trough, and the portion within the circle is ground down so that its level is about 0.1 mm. below that of the slide. When a drop of liquid is placed within the circle and covered with a cover-glass, the liquid spreads out into a thin layer, every part of which can be examined under the microscope. A ring of vaseline is placed along the edge so as to prevent evaporation. By flaming the slide and cover slip, and using sterile liquid the preparation can be observed for several days if need be. This method is especially to be recommended for studying trypanosomes, malaria parasites, etc.

Staining of Bacteria.—In order to obtain good stains it is necessary to have good clean cover-glasses. The cover-slips, as purchased in the market, are unfit for use until they have been cleaned. One method of doing this is to heat the slips in a beaker with concentrated sulphuric acid and potassium bichromate. The cover-glasses are then washed in running water, after

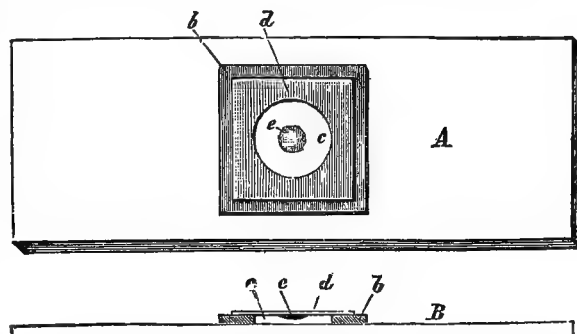


FIG. 5118.—Cell Slide showing Hanging Drop. *A*, Surface view; *B*, side view; *b*, edge of cell *c*; hollow of cell; *d*, cover glass; *e*, hanging drop.

which they are kept in alcohol. Another procedure which gives very satisfactory results is to soak the cover-glasses first in alcohol, after which they are wiped with soft, washed linen, placed in an Esmarch dish and heated in a dry-heat sterilizer at about 200° for an hour or two. This high heat completely destroys the organic matter that may be on the glasses. A cover-glass is not clean

if a small drop of water, when spread over the surface, does not remain even, but gathers into droplets.

Several kinds of forceps have been devised for holding cover-glasses while staining. The Cornet forceps (Fig. 5119, *a*) is well known, and

is useful though rather awkward. Stewart's modification is widely used (Fig. 5119, *b*). A much more convenient forceps is shown in Fig. 5119, *c*. The lower blade has a thin edge which permits one to pick up the cover-glass without contact with the fingers. The upper blade is bent in order to avoid capillarity, and is narrowed to a point so that the specimen is held by point contact. A catch serves to hold the cover-slip in place.

Aniline Dyes.—The aniline dyes which are employed for staining purposes are either basic or acid in character. The former contain amido groups and are spoken of as nuclear stains, since they color the nuclei of cells as well as bacteria. The

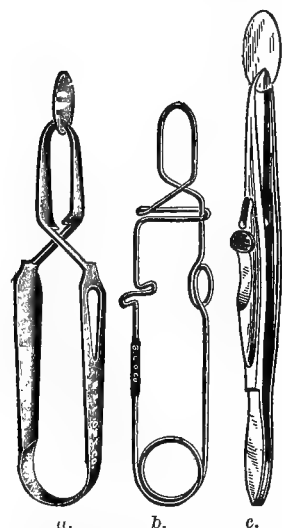


FIG. 5119.—Cover-glass Forceps. *a*, Cornet's; *b*, Stewart's; *c*, Novy's.

latter contain hydroxyl groups and do not stain bacteria but are used chiefly for contrast coloring, and to some extent for decolorizing. The basic dyes are usually employed as salts of hydrochloric acid, while the acid dyes occur as sodium or potassium salts.

Among the basic aniline dyes which are commonly employed may be mentioned fuchsin, gentian violet, methyl violet, crystal violet, methylene blue, thionin, safranin, methyl green, neutral red, and vesuvium or Bismarck brown. These are all more or less crystalline powders, and while some are definite chemical compounds, others are mixtures. For this reason various brands are met with on the market, and it will be readily understood why the exact duplication of stains is not always possible.

It is advisable to keep on hand not only the solid dyes, but also stock solutions which are saturated alcoholic solutions. The amount required to saturate will vary from two to five per cent.

The concentrated alcoholic solutions are never used as such, but serve for the preparation of the dilute dyes which are the stains proper. The latter are made by placing a few cubic centimetres of the concentrated dye in a small tincture bottle, and adding ten to twenty parts of water. This bottle is then provided with a cork and a piece of glass tubing which serves as a pipette. The different dilute dyes can be kept in a stand, such as is shown in Fig. 5120. The dilute dyes after a while undergo alteration and yield deposits. In that event they should be filtered before use, or else new dilutions should be made.

The acid aniline dyes are represented by eosin, acid fuchsin, and fluorescein. The concentrated and the dilute dyes are prepared as above.

The staining solutions may be used as such, or their properties may be accentuated by the addition of substances which act more or less directly as mordants. A number of these solutions are in daily use, and for that reason their preparation is here given.

Löffler's methylene blue is made by adding 30 c.c. of concentrated methylene blue to 100 c.c. of a 0.01-per-cent. solution of potassium hydrate. A similar solution with less alkali was first used by Koch. The alkali not only serves to make the cell more permeable, but also

increases the staining power by liberating the free base from the dye.

Carbolic fuchsin, or Ziehl solution, is made by adding 1 gm. of fuchsin and 10 c.c. of alcohol to 100 c.c. of a five-per-cent. carbolic-acid solution. The stain is very widely used for simple as well as double staining. Czaplowski modified it by substituting glycerin for the alcohol. His solution is prepared by rubbing up in a mortar 1 gm. of fuchsin with 5 gm. of carbolic acid, and to this 150 gm. of glycerin and 100 c.c. of water are added.

Carbolic methylene blue, first employed by Kühne, consists of 1.5 gm. of methylene blue, 10 gm. of absolute alcohol, and 100 c.c. of a five-per-cent. solution of carbolic acid.

Carbolic thionin consists of 10 parts of a saturated solution of thionin and 100 parts of a one-per-cent. solution of carbolic acid (Nicolle).

Carbolic gentian violet is made the same as the preceding (Nicolle).

Aniline Water, Gentian Violet, etc.—The carbolic acid, like the alkali, favors the penetration of the stain. Aniline water acts in like manner and was first used by Ehrlich. To prepare the aniline water a few cubic centimetres of aniline is placed in a test tube, and this is then filled with distilled water and thoroughly shaken. The milky liquid is filtered through a moist filter. To the water-clear filtrate enough concentrated fuchsin or gentian violet is then added to make the liquid opaque, and so that it just begins to form on the surface a slight metallic film of precipitated dye. The solution is then used as such, but if the deposit is very marked it may be necessary first to filter it. The aniline-water dyes do not keep very well, and for that reason it is well to make a fresh solution every time that it is to be used. Oil of cloves has been suggested by London as a substitute for aniline.

The aniline-water stains were first employed by Ehrlich for coloring the tubercle bacillus, and are still used for that purpose. They are, however, employed especially for staining whips and in connection with Gram's stain. In the latter case, after the preparation has been stained with the solution, a mordant is applied, known as Lugol's solution, which serves to form a difficultly soluble compound between the dye and the cell contents.

Lugol's solution consists of 1 part of iodine, 2 parts of potassium iodide, and 300 parts of distilled water.

The Staining of Cover-glass Preparations.—These may be considered under the head of (1) simple, (2) double, and (3) special stains. For the simple stains, when it is desired to have a heavily colored preparation, either fuchsin or gentian violet is used. When it is desired to bring out structural characteristics, it is advisable to employ solutions which stain more feebly, such as methyl-

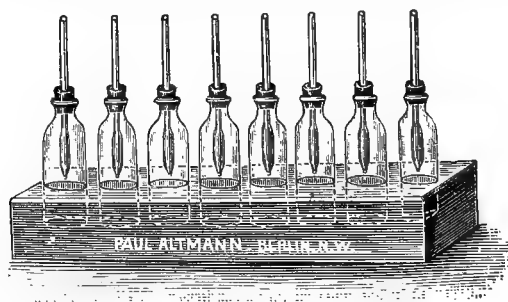


FIG. 5120.—Stand for Staining Solutions.

ene blue or thionin. In either case the simple or reinforced stains, given above, may be employed.

To make a stained preparation of a pure culture the procedure is as follows: A drop of water, preferably distilled, is placed upon a clean cover-glass, which either lies on a board or is held in a pair of forceps. By means of a sterile platinum wire a minute amount of the bacte-

rial growth is picked up and transferred to the water. Only enough should be added so as to impart to the water a slight cloudiness. The remainder on the wire is then burned off. The drop is then spread over the whole surface of the glass and allowed to dry in the air, or the process may be hastened by passing it above a flame. Care must be taken not to dry too rapidly as, in such case, vacuolation of the protoplasmic contents of the cell results. The air-dried preparation must now be fixed in order that the bacteria may not be washed off in the subsequent treatment. The fixing is done by passing the cover-glass three times through a flame. Care must be taken not to scorch the specimen, for in that case the dye will not act. It is well to turn down the flame so that it is at most but two inches high. The properly fixed cover-glass is now covered with the stain, which is allowed to act for ten to twenty seconds. The dye is then washed off under the tap and the cover-glass inverted upon a glass slide. Any water which may be on the surface of the slip should be removed by means of a piece of filter paper. The preparation can now be examined under a No. 7 objective, or with the one-twelfth-inch oil immersion lens. If the specimen is such as to merit preservation a drop or two of water may be applied to the edge, and in this way the slip can be floated off without damaging the film. The excess of water can then be touched off with a piece of filter paper, after which the specimen is dried in the air or by passing it over the flame. The thoroughly dried film is then inverted upon a drop of Canada balsam placed on the centre of a clean slide. By gentle warming or by pressure the balsam can be made to spread out evenly.

Smear or streak preparations made from the fluids or organs of the body are stained in the same way. The fixation of the cover-glass when it contains much proteid matter, as in the case of blood streaks, requires special care. The best results are obtained by immersing the slip for a few minutes in a mixture of equal parts of absolute alcohol and ether. Fixation is thus accomplished without any injury to the blood cells. It is sometimes advisable, instead of adding the dye to the cover-glass, to float the latter upon the dye in a watch-glass.

To make good blood preparations requires considerable care and experience. A small drop of blood is placed on a perfectly clean cover-glass, which is held in a pair of forceps. A second cover-slip is then applied, evenly and without pressure, and as soon as the blood has spread out the two glasses are drawn apart. The blood cells must not be crushed and should lie in a single layer.

The smears from the cut surface of an organ are made by gently applying the cover-glass, without pressure, and then drawing it away; or a piece of the organ may be taken up in the forceps and streaked over the cover-glass, care being taken to leave only the thinnest film possible.

The ordinary glass slide is often used in place of the cover-glass. The streaks or blood smears are made as in the case of the latter. When the growth is hard, as in the case of actinomyces, it is well to crush it between two glass slides.

Double Staining.—This procedure is resorted to when staining the tubercle bacillus and the allied acid-resisting bacilli. It is also used for staining spores, and in differentiating bacteria by means of Gram's stain. Other special methods are given under gonorrhoea and meningitis.

The group of acid-resisting bacilli, the type of which is the tubercle bacillus, are stained with more or less difficulty by the simple stains. The dye, however, can be forced into the cell by the aid of heat, and especially if the reinforced stains, such as carbol fuchsin or aniline-water gentian violet, are used. On subsequent treatment with acid and alcohol the ordinary bacteria which chance to be present are readily decolorized, whereas the acid-resisting retain the stain. A contrast

color, such as methylene blue, will then stain the background and the ordinary bacteria a light blue.

Staining of the Tubercle Bacillus.—The cover-glass is air-dried and fixed in the usual manner, after which any one of several methods may be used. The *Ziehl-Neelsen* method is usually employed. It is carried out as follows: The cover-glass, held in the forceps, is covered with carbol fuchsin and heated over the flame so that vapors are given off for one or two minutes. It is then rinsed in water and dipped for a few seconds in a twenty-per-cent. solution of nitric acid, after which it is washed in dilute alcohol (sixty per cent.) till it is almost colorless. Methylene blue is then applied for a few seconds and washed off. The specimen is transferred to a slide, the surface dried, and examined under the microscope. The tubercle bacilli will appear red on a blue background. The ordinary bacteria will appear blue.

The *Koch-Ehrlich* method consists in staining with aniline-water fuchsin or gentian violet with the aid of heat for a few minutes. The specimen is then decolorized in thirty-five-per-cent. nitric acid for about a quarter of a minute, washed in dilute alcohol till nearly colorless, after which methylene blue or Bismarck brown is applied for a contrast color.

In the *Fraenkel-Gabbet* method the preliminary staining is effected with carbol fuchsin as above. The decoloration and contrasting is done at once by immersing the cover glass in a saturated solution of methylene blue in the following: Sulphuric acid 25 parts, alcohol 50 parts, distilled water 1,000 parts. It is then rinsed with water and examined.

Czaplewsky's method differs from the preceding in the way the decoloration is effected. He employed for this a solution of 1 gm. of fluorescein and 5 gm. of methylene blue in 100 c.c. of alcohol. The specimen is first stained with carbol fuchsin; then, without rinsing in water, it is placed for a few seconds in the fluorescein methylene blue solution. Finally it is dipped ten or twelve times in a solution of 5 parts of methylene blue in 100 parts of alcohol. It is then washed with water and examined.

Numerous modifications of these methods have been proposed, but they possess no special advantage over those given.

Staining of Spores.—The cover-glass preparation is treated for some minutes with hot carbol fuchsin, either on the forceps or by floating on the dye. It should then be rinsed and examined in water. If the spores are colored, the next step is taken; if not, then the heating with the dye is continued until they are stained. The specimen is then decolorized in dilute acid and alcohol until the spores stand out red on a colorless background. Methylene blue is then applied for a contrast, washed off, and the preparation is ready for examination. The bright red spores are seen within the light blue cells. This method requires considerable care, and every step must be controlled by frequent examinations under the microscope.

In order to enable the dye more readily to enter the spore, Möller treated the cover glass, first, for a minute or two with a five-per-cent. solution of chromic acid, after which essentially the above procedure was followed. By repeated passage through the flame or by heating with strong sulphuric acid for a few seconds the substance of the spore can be disintegrated so that on subsequent staining with carbol fuchsin the spores will readily take the dye. This treatment, however, destroys the original cell, and hence contrast coloration is not possible.

Klein varies the procedure of spore staining given above by adding an equal volume of carbol-fuchsin solution to a suspension of the spore-bearing organism in physiological salt solution. The mixture is gently warmed for six minutes. Cover-glass preparations are then made, dried, and fixed. It is then decolorized in one-per-cent. sulphuric acid solution, and counterstained in the regular manner. This method may be useful in staining those varieties which are especially resistant.

The Gram Stain.—This is one of the most valuable

methods in bacteriology, since it often serves to distinguish between organisms which otherwise resemble each other very closely. The cover-glass preparation is floated for a few minutes on aniline-water gentian violet or on carbolic gentian violet. Heat may be applied, but in that case the excessive staining will interfere with the subsequent decoloration. The specimen is then rinsed in water and immersed in Lugol's iodine solution for two or three minutes. After rinsing in water it is then placed for a few minutes in strong alcohol until most of the dye has been washed out. Very dilute eosin solution is now applied for about five seconds. After thorough washing with water it is ready for examination. The organism will appear a deep violet on a pink background.

Gram's method is applicable to the bacilli of anthrax, symptomatic anthrax, diphtheria, leprosy, malignant cedema, mouse septicæmia, rouget, tetanus, tuberculosis, the Fraenkel diplococcus, *Micrococcus tetragenus*, the various staphylococci and streptococci, actinomycetes, moulds, and yeasts. It is not given by the bacillus of glanders, typhoid fever, hog cholera, Asiatic cholera, chicken cholera, influenza, plague, Friedländer's bacillus, colon bacillus, gonococcus, rhinoscleroma, and recurrent fever spirillum.

The Staining of Flagella.—Special care must be given to the preparation of the cover-glass. The cultures should be made on freshly inclined, moist agar, and should, as a rule, be less than twenty-four hours old. A very dilute suspension of the growth is made, and when spread over the cover-glass is allowed to dry in the air. The fixation must be done with the least amount of heat possible. This can best be done by passing the cover-glass, held between the thumb and forefinger, through the flame.

In Löffler's method the specimen is covered with a mordant solution which consists of 100 parts of a twenty-per-cent. tannic-acid solution, 50 parts of a cold saturated ferrous-sulphate solution, and 10 parts of alcoholic fuchsin. The cover-glass is heated over the flame so that vapors are given off for a minute or two. Every trace of the mordant must then be removed by washing with water, and if it has dried down around the edge it should be removed with a knife. The last traces of the mordant can be removed by momentary immersion in absolute alcohol. The specimen is then heated with aniline-water fuchsin for a couple of minutes, washed with water, and examined. The chief difficulty in this method lies in the formation of a heavy deposit of foreign matter, which masks the bacteria.

Fischer's mordant is a slight modification of that of Löffler. It consists of 2 gm. of dry tannin, 20 c.c. of water, 4 c.c. of ferrous sulphate (1:2), and 1 c.c. of concentrated alcoholic fuchsin. The aniline water fuchsin is made by adding about 5 gm. of fuchsin, and 1 c.c. of a one-per-cent. solution of sodium hydrate to 100 c.c. of aniline water.

Bunge employed a mordant consisting of 75 parts of concentrated tannin solution, 25 parts of a five-per-cent. solution of ferric chloride, and 10 parts of a concentrated aqueous fuchsin solution. After standing some days hydrogen peroxide is added until a reddish-brown color is obtained.

Pitfield makes use of a single solution of mordant and dye. Two solutions are first prepared: (1) consisting of 1 c.c. of saturated alcoholic gentian violet and 10 c.c. of saturated aqueous alum; (2) consisting of 1 gm. of tannic acid and 10 c.c. of distilled water. The two solutions are filtered and then combined. The mixture is heated on the cover-glass over a flame for about a minute, and then washed off.

Van Ermengem's method is essentially different. The cover-glass is warmed for about five minutes with a fixing solution consisting of 60 c.c. of a twenty-per-cent. tannin solution, 30 c.c. of two-per-cent. osmic-acid solution, and four to five drops of glacial acetic acid. It is then washed with water, rinsed in alcohol, and dipped for one or two seconds in a sensitizing solution of silver

nitrate (one-half to one per cent.). After this it is placed for a few seconds in the reducing solution which consists of 5 parts of gallic acid, 3 parts of tannic acid, 10 parts of sodium acetate, and 350 parts of distilled water. It is again placed in the silver-nitrate solution, in which it is moved about until the liquid darkens, after which the preparation is washed with water, dried, and examined.

Of the numerous other modifications which have been proposed that of Gemelli only need be given. Gemelli cleans the cover-glasses in a boiling mixture of potassium bichromate (three per cent.), and sulphuric acid (five per cent.). After washing in water they are kept in alcohol. Before use each cover-glass is flamed several times. Gelatin cultures developed at 37° C. are said to give the best results. A loopful is transferred to 5 c.c. of water in a watch-glass, and from this suspension a drop is taken and spread over a cover-glass, which is then set aside over calcium chloride to dry. The specimen is then placed for ten to twenty minutes in a one-fourth-per-cent. solution of potassium permanganate. The preparation is now washed well in distilled water, after which it is placed in a three-fourths-per-cent. solution of calcium chloride, to which has been added a one-per-cent. solution of Gruber's neutral red in the proportion of twenty to one. After remaining in this for fifteen to thirty minutes the specimen is washed, dried, and mounted. The method is said to give excellent and sure results without the annoying precipitates which form in the other procedures.

Staining of Capsules.—Welch's method consists in treating the cover-glass with glacial acetic acid for a few seconds. The excess of acid is drained off with filter paper, after which the specimen is washed in aniline water gentian violet, and finally in a sodium-chloride solution (0.85 to 2 per cent.). The heavily stained bacillus will be found to be surrounded by a pale violet halo.

Nicolle treats the cover-glass with a mixture of one-per-cent. carbolic acid (100 parts) and concentrated glacial alcoholic gentian violet (10 parts). It is then washed in absolute alcohol containing one-third its volume of acetone, rinsed in water, dried, and mounted.

Hiss' copper-sulphate method consists of preparing films by mixing the organism with a drop of diluted serum on a cover-glass. If the organism has been grown upon ascitic or serum medium, this latter step is not necessary, the film being made direct from culture. The film is dried in air and fixed with heat. An aqueous solution of gentian violet (5 c.c. saturated alcoholic solution gentian violet to 95 c.c. distilled water) or fuchsin may be used, as stain. The stain is placed on the fixed cover-glass preparation, and carefully heated over a flame for a few seconds until steam arises. The stain is then washed off with a twenty-per-cent. solution of copper sulphate (crystals). Thoroughly dry the stained preparation between filter papers and mount for examination.

Staining of the Babes-Ernst Granules.—Neisser recommends the following method as a means of differentiating the diphtheria bacillus from like organisms. A culture grown on Löffler's serum should be used. The specimen is treated for one to three seconds, or a little longer, with the following solution: 1 gm. of methylene blue, 20 c.c. of absolute alcohol, 50 c.c. of glacial acetic acid made up to one litre with distilled water. It is then washed with water and stained with Bismarck brown (two-per-cent. aqueous solution) for three to five seconds. Finally it is washed with water and examined. The blue granules will stand out in the light brown bacilli.

Piorkowski heats the preparation for one-half to one minute with an alkaline solution of methylene blue, then decolors for five seconds in alcohol containing three per cent. of hydrochloric acid. A one-per-cent. aqueous eosin is applied for contrast, after which the preparation is washed and examined.

Impression Preparations of Colonies.—It is very often

desirable to reproduce or preserve the characteristic surface colonies. The selection of the surface colony is made under the microscope, after which the tube of the instrument is raised and a cover-glass is dropped down upon the colony. Gentle pressure is applied, the cover-glass lifted off, air-dried, fixed, and stained with methylene blue in the usual way.

Staining of Protozoa.—The study of the protozoa and kindred microorganisms is so closely associated with bacteriological methods that it will not be amiss to discuss briefly the more useful stains employed in connection with this important class. Many advances have recently been made along this particular line of work which has thrown much light upon diagnosis and the etiology of disease.

Romanowsky's Chromatin Stain.—This method is extremely valuable for staining protozoal parasites, such as those of malaria and the trypanosomes. It may also be used for staining *Spirochæta pallida*. When properly carried out it gives an admirable differentiation of the chromatin, which appears red on a blue background. Nocht's modification gives very good results, and is briefly as follows: A solution of one-per-cent. methylene blue and one-half per cent. sodium carbonate is kept at about 60° C. for several days to "ripen." The change which takes place is one of slow oxidation, and as a result a number of products form, among which is the one which is essential to this method. This active red constituent has been designated as methylene azur. To about 2 c.c. of water in a watch-glass two to three drops of a one-per-cent. solution of eosin are added, and then the altered blue, drop by drop, till the eosin tint just disappears. The specimen is floated on this dye for five to ten minutes, after which it is washed and examined.

Independently Wright, Leishman, and Reuter arrived at a simple modification. The ripened or polychrome methylene blue is treated with an eosin solution to slight excess. The precipitate, which Reuter has called a methylene-blue eosin, is then filtered, washed, and dissolved in methyl alcohol. This solution can now be obtained from Grüber. Thirty drops of this are added to 20 c.c. of distilled water in a large watch-glass or Petri dish. The specimen, which can be fixed with ether alcohol or with formaldehyde alcohol (10:90), is immersed in the dye for fifteen to thirty minutes. It is well gently to agitate the liquid from time to time. It is then washed, dried, and mounted.

Wright's modification has been recommended by Musgrave and Clegg as giving the best results in staining the amœba of the dysentery. The Leishman stain has been prominently brought forward by Wright and Douglass in their staining of white blood cells (phagocytes) while studying the opsonic action of blood serum. As a phagocytic cell stain, this apparently possesses no advantage over Wright's or certain other modifications of the Romanowsky stain. These stains, ready for use, can be procured from dealers.

Laveran employs 1 c.c. of a one-per-cent. solution of azur, 2 c.c. of a 0.1-per-cent. solution of eosin, and 8 c.c. of water. The specimen is stained for ten minutes, then washed and immersed for two or three minutes in a five-per-cent. tannic solution, after which it is washed, dried, and mounted.

Giemsa has made several modifications of the stain. The following is one, which, in the hands of Williams and Lowden, has given excellent results in the study of the finer morphological characteristics of "Negri bodies."

Take azur II—eosin, 3.0 gm.; azur II., 0.8 gm.; glycerin (Merck's chemically pure), 250.0 c.c.; methyl alcohol (chemically pure), 250.0 c.c. Both glycerin and alcohol are heated to 60° C. The dyes are put into the alcohol, and the glycerin is added slowly, stirring. The mixture is allowed to stand at room temperature over night, and, after filtration, it is ready for use.

The technique followed by Williams in the study of "Negri bodies" was to prepare smears of brain tissue

(cortex from near the fissure of Rolando, Ammon's horn, and cerebellum), and air-dry. Fix in methyl alcohol for five minutes. The stain is added to distilled water, which has previously been made alkaline by the addition of one drop of a one-per-cent. solution of potassium carbonate to each 10 c.c. of the water. The stain is used in the proportion of one part of stain to one part of the slightly alkaline water. This solution is poured over the fixed smear at once, and allowed to stand from one-half to three hours, but a longer time brings out the structure better. The stain is washed off in running tap water from one to three minutes, and dried between fine filter papers. In this method of staining, the cytoplasm of the "bodies" stains blue and their central bodies and chromatoid granules stain a blue-red or azure.

Giemsa's stain has been used extensively to bring out *Spirochæta pallida*, in the examination of material from syphilitic lesions. Film preparations are prepared and fixed in absolute alcohol for fifteen or twenty minutes, then dried with filter paper. The technique is continued in practically the same manner as mentioned above in the staining of "Negri bodies," but the staining solution should not be left on the film more than fifteen minutes. It is then washed, dried between filter papers, and mounted in balsam. The *Spirochæta pallida* takes somewhat of a faint reddish tint, while the frequently associated *Spirochæta refringens* takes a bluish tint like other organisms.

Goldhorn's Modification.—Goldhorn has prepared a polychrome-methylene-blue eosin stain which gives excellent results in the staining of film preparations of *Spirochæta pallida*. This stain has the advantage of being easily and quickly made. The method is as follows: Dissolve 2 gm. of lithium carbonate in 200 c.c. of water and add 2 gm. methylene blue (Merck's medicinal, Grüber's B.X., or Koch's rectified). Moderately heat the mixture in a rice boiler until a rich polychrome is formed,—this is recognized by a distinct red coloration of the fluid. Allow to cool gradually, and then remove the undissolved residue by filtering through cotton. To one-half of the alkaline filtrate add sufficient five-per-cent. acetic-acid solution to give a distinct acid reaction recognized by a red color above the line of discoloration on the litmus test paper. The other half is now added to bring the whole back to a slight degree of alkalinity. A one-half-per-cent. solution of French eosin is gradually added, stirring until a filtered sample shows a pale bluish color with slight fluorescence. Allow to stand one day, then filter through a double piece of filter paper to collect the precipitate which has formed. Dry the precipitate on the filter paper at room temperature. When thoroughly dry, the precipitate is removed from the filter paper and dissolved in commercial wood alcohol. The alcoholic solution is allowed to stand for one day in an open vessel, then the insoluble residue is removed by filtration. The stain is now ready for use.

The staining technique is as follows: Smears of serum or blood from freshly cuffed lesions are made upon clean slides. To the unfixed preparation add sufficient stain to cover well, allow the dye to act for three to four seconds, then pour off the excess. The slide is slowly immersed in water (film side down, to keep free from resulting precipitate) thus permitting an interaction between the water and the dye. It is held quietly in the water for four to five seconds, then moved about to wash off excess of stain. Dry and examine with oil immersion. *Spirochæta pallida* takes a violet stain, which may be changed to a bluish-black by adding Gram's iodine solution for fifteen to twenty seconds. The regular staining requires only ten to twelve seconds for completion, thus affording a good working method for rapid laboratory diagnosis.

Stern's Silver Impregnation Stain for Spirochæta Pallida.—Stern has quite recently succeeded in staining *Spirochæta pallida* in smear preparations by a silver-impregnation process.

He makes the stain by preparing, upon slides, smears

of material from syphilitic lesions, and allowing them to air-dry at 37° C. for some hours. The fixed preparations are placed in a ten-per-cent. silver-nitrate solution for several hours. The solution should be in a colorless glass vessel, and allowed to stand in diffuse sunlight during the staining of the specimen. When the preparation takes a certain brownish tone (easily recognized after some experience) and shows a metallic sheen, it should be removed from the silver solution. Wash thoroughly with water, dry, and prepare for examination. Blood cells are well preserved. They show a delicate black contour and certain fine granules. The spirochetes take a deep black on a pale brown or in places a colorless background.

Staining of Sections.—In order to study the finer distribution of bacteria and certain protozoa in the body of an infected subject it is necessary to harden portions of the different tissues and organs, which are then cut up into sections. The tissue may be cut by the aid of a freezing microtome, but the best results are obtained when the material is embedded in celloidin or in paraffin. The latter is especially to be recommended. The methods which are used for this work are essentially histological, and need not be considered in this connection.

Staining of Bacteria in Tissues.—To obtain a simple stain for bacteria the section is placed in the dilute aniline dye for about five minutes. Dilute carbolie fuchsin or carbolie methylene blue is very good for this purpose. It is then washed thoroughly in water and transferred to very dilute acetic acid (1 c.c. of glacial acetic acid to 1,000 c.c. of water). The section is now placed in strong alcohol for one-half to one minute to remove the excess of dye. After washing in water it may be examined, and if the decoloration has not been sufficient, the treatment with alcohol can be repeated. When properly differentiated the section is placed for a few seconds in absolute alcohol for dehydration, then cleared in oil of cloves, passed through xylol, and mounted in Canada balsam.

In Kühne's method the sections are stained in carbolie methylene blue and differentiated in one-half per cent. hydrochloric acid, rinsed in dilute lithium-carbonate solution, then in water. The section is transferred to absolute alcohol, which is slightly colored with methylene blue for one-half minute; then for a few minutes to aniline oil containing methylene blue, finally into clear aniline oil, turpentine, xylol, and balsam.

Nicoll stains the sections in carbolie thionin, washes in water for about a minute, dehydrates with absolute alcohol, clears up in oil of cloves, and mounts in balsam. Another procedure employed by him is to stain first with Löffler's methylene blue, differentiate in one-half per cent. acetic acid, and fix in ten-per-cent. solution of tannin for a few seconds. The section is then washed, dehydrated, cleared, and mounted.

Gram's stain is applied to sections in the following manner: The section is placed in the freshly prepared aniline-water gentian violet for about ten to fifteen minutes, after which it is washed in water, or better in aniline water, to remove the excess of dye. The section is then placed in Lugol's iodine for three to five minutes, transferred to absolute alcohol, in which it is tilted about until the excess of the stain has been removed and only a pale violet color remains. Ebner's solution may also be used for decolorizing. It is counterstained in very dilute eosin for about a minute, washed in water, dehydrated in absolute alcohol, cleared in cloves, and mounted.

Bismarck brown may be used for a contrast color, or Weigert's picrocarmine. The latter may be made by adding 1 part each of carmine and ammonia to 50 parts of water; to this solution picric acid is added until a precipitate forms which is dissolved by the addition of a little ammonia; finally a few drops of carbolie acid are added.

Tubercle and leprosy bacilli can be stained in sections by applying the principle employed for cover-glass

preparations. The carbolie fuchsin should be warmed to about 40° C. in a Petri dish. The sections remain in this solution for fifteen to thirty minutes, after which they are washed in water to remove the excess of dye. They are then decolorized in dilute acid, or better in Ebner's solution. The latter consists of one-half part each of sodium chloride and hydrochloric acid, 30 parts of water, and 100 parts of alcohol. The faint pink sections are then placed in Löffler's methylene-blue solution for about half a minute, after which they are dehydrated in absolute alcohol for a few seconds, transferred to xylol, and mounted in balsam.

Staining of Protozoa in Tissues.—It will not be necessary to include under this classification other organisms than the *Spirochæta pallida*. As this spirochete is almost constantly associated with syphilis, it is now commonly accepted as the etiological factor of the disease. Several methods have been used for the demonstration of *Spirochæta pallida* in section, but that most commonly used is the first method of Levaditi. This method is essentially a modification of Ramon y Cajal's method for the silver impregnation of nerve fibrillæ. Levaditi proceeds as follows: Small pieces of tissue about 1 mm. in thickness are "fixed" in ten-per-cent. formol for twenty-four hours. Wash and harden in ninety-six-per-cent. alcohol for twenty-four hours. Remove and wash in distilled water until the tissue sinks in the water. Impregnate with silver by placing in a solution of 1.5–3.0 per cent. of silver nitrate, and keeping at a temperature of 38° C. for three to five days. When taken out the tissue is quickly washed in distilled water, and placed in the following silver reducing solution: Pyrogallie acid, 2–4 gm.; formol, 5 c.c.; distilled water, 100 c.c. Allow to stand in the reducing solution at room temperature from twenty-four to forty-eight hours. Remove and wash in distilled water, dehydrate in absolute alcohol; xylol; embed in paraffin, and cut in sections not more than five microns in thickness. The tissues may be counterstained by Giemsa mixture, or by toluidin blue, then cleared and dehydrated by the regular histological method. In either case, the spirochetes, in a well-stained section, should appear almost black in color.

While the method just given is longer, it is perhaps more reliable than the later modification by the same author. In the second method the tissue in thin pieces is fixed in ten-per-cent. formol for twenty-four to forty-eight hours, then hardened in ninety-six-per-cent. alcohol for twelve to sixteen hours; removed and washed in distilled water. Impregnate at room temperature from two to three hours, then at a temperature of about 50° C. from four to six hours, in a solution compound of silver nitrate one per cent.; pyridin, ten per cent. (added just before using); distilled water, 100 c.c. During the process of impregnation, the solution should be kept in a well-stoppered flask. Remove tissue and rapidly wash in a ten-per-cent. pyridin solution. Reduce the silver in tissue by placing in a solution compound of pyrogallie acid, four per cent. (added just before using); acetone (purest), ten per cent.; pyridin, fifteen per cent.; distilled water for 100 c.c. The reduction is completed after a few hours. Harden in alcohol, xylol, paraffin, section. The advantage of this method over the former lies in the comparatively short time in which it may be performed. But, generally, it does not give as uniformly good results as the first method.

DIAGNOSTIC METHODS.—The general principles which have been given find their practical application in the diagnosis of disease. It is desirable, therefore, to indicate briefly the way in which these methods are applied.

1. *Actinomyces* (streptothricosis).—This condition is not, as was first supposed, due to one definite organism, but to several closely related species. Culture and staining characteristics aid in differentiation. Some species take the "acid-fast" stain, while others do not. The pus should be examined unstained under a cover-glass for the characteristic yellowish, radiating masses with club-shaped threads along the border. Perma-

nent preparations may be made by making smears, and staining either by the simple or by the Gram method. The pus may be hardened in mercuric chloride, sectioned, and stained by Gram. Curettings may be treated in like manner.

2. *Anthrax*.—Cover-glass smears of the blood, fluid from vesicles, or scraping from pustules are stained by the simple and by the Gram method. Confirmation of the nature of the organism found can be obtained by inoculating a white mouse or a guinea-pig subcutaneously with the material. This with the cultural characteristics will enable identification.

3. *Bubonic Plague*.—This diagnosis may be made during life, but more often after death. In the pneumonic form the blood-streaked sputum can be used for simple stains, which will show large numbers of the small rods. In the bubonic type the enlarged gland may be punctured and thus material obtained for examination. The detection of the bacillus in the blood can be effected by drawing several cubic centimetres of the blood from a vein by means of a syringe. Agar plates, one part of blood to two parts of agar, should then be made. Whether the result is apparently positive or wholly negative, an animal experiment must be carried out. The suspected material is inoculated subcutaneously into a guinea-pig, and if plague bacilli are present, death will ensue in from five to eight days. Cultures and smears from the animal will then establish the nature of the organism. An important cultural characteristic is brought out by planting the material on agar containing about three per cent. of salt. Round or pear-shaped involution forms develop. The smears from the body should be stained with Löffler's methylene blue or with carbollic thionin. The short rods take the bipolar stain, and if the material is old, roundish involution forms or "doughnuts" will be met with. The bacilli are not stained by Gram.

4. *Cholera*.—The examination may aim to find the cholera vibrio in the drinking-water, or it may be concerned with the diagnosis of the disease. In the latter case the rice-water discharges should be collected and searched for mucous flakes. Preparations from these, when stained, will show the appearance of the characteristic vibrio. The appearance of the colonies on gelatin and on agar plates, the growth in bouillon, and the indol reaction serve to identify the organism. The intraperitoneal injection of the culture into a guinea-pig should also be practised. The most important reaction is that of Pfeiffer. It consists in injecting into the peritoneal cavity of a guinea-pig a mixture of the cholera antiserum and the suspected organism. Every few minutes a drop of fluid is withdrawn from the peritoneal cavity by means of a capillary tube and examined. If the organisms persist, it is safe to say that they are not those of true cholera. The latter under these conditions lose motion, become granular, and soon disappear.

It may be possible under exceptional circumstances to detect the cholera vibrio in drinking-water by ordinary plating on gelatin. Obviously the number of the organisms may be so small and the other bacteria may be so numerous that it is impossible to obtain positive results by this method. To overcome this difficulty Schottelius devised an enriching method. This consists in adding the suspected water to a one-per-cent. solution of peptone and incubating at 37° C. for about twelve hours. The actively motile cholera spirilla, on account of their need of oxygen, accumulate as a cloudy layer near the surface. A loop of this liquid is then transferred to and spread over the surface of gelatin and agar plates, and the further identification is then easily effected. Obviously the peptone may be added direct to the water, for example 100 c.c., and in this way the presence of a very few vibrios in a large volume of water may be detected.

5. *Diphtheria*.—The necessary material for the examination is obtained either by means of a Roux spatula (Fig. 5095) or by a cotton swab. The cotton swab is usually employed, and is made by twisting a piece of cotton about the end of a thick iron wire. The wire

should be about six inches long. The cotton end is then placed in a plugged test tube which is sterilized by dry heat. Whether a pseudomembrane is present or not, scrapings are made from the surface of the affected tonsils or throat and examined. Usually the swab is streaked over the surface of one or more tubes of plain, or better Löffler's serum. These tubes are incubated over night and examined in the morning for the characteristic diphtheria bacilli. The cover-glass preparations from these cultures are stained with Löffler's methylene blue. The swollen rods with irregularly stained contents are easily identified. In case there is any doubt as to the diagnosis, it is advisable to inoculate a guinea-pig with the culture material.

Whenever possible it is advisable to make cover-glass preparations direct from the false membrane. These are then stained with Löffler's methylene blue. The diagnosis can thus often be made in a few minutes.

6. *Dysentery*.—It is necessary to distinguish between two types, the bacillary and the amoebic. The examination for amoebæ should be made at once, immediately after the stool is passed, in order to obtain actively motile organisms. A drop of the thin faeces or suspension is placed on a slide, covered with a cover-glass, and examined under the microscope. The characteristic motion will leave no doubt as to the nature of the organism. The motion can be observed best on a warm slide or in an incubator. Staining is not necessary.

The bacillary form is due to the *Bacillus dysenteriae*, and the diagnosis of this type necessitates the detection of this organism. Make lactose litmus agar plates from faeces and develop at 37° C. *B. coli* colonies may be excluded by their acid formation. From the colorless colonies which develop after twenty-four hours, subcultures should be made upon glucose agar, mannitolitmus agar, etc., for differentiation. Those which cause gas formation in glucose agar may be rejected. The pure cultures should finally be tested for agglutination with the serum of a dysenteric patient. Too much care, however, cannot be exercised in drawing conclusions based upon a positive agglutination reaction, since this test is undoubtedly given by allied organisms.

7. *Gonorrhœa*.—Cover-glass preparations made from the pus will serve to establish the diagnosis in nearly all instances. They should be stained with Löffler's methylene blue. A fair double stain can be obtained by first applying eosin, after which the blue can be used for a few seconds. The result is a more or less pink background with blue gonococci. Gram's method is negative.

Von Wahl recommends the following method of double staining which brings out the gonococci as reddish-violet to black cells on a light green background. The stain consists of: Concentrated alcoholic solution of auramin, 2 c.c.; ninety-five-per-cent. alcohol, 1.5 c.c.; concentrated alcoholic solution of thionin, 2 c.c.; concentrated aqueous methyl green, 3 c.c.; water, 6 c.c. The auramin and thionin solutions are prepared by dissolving the dyes in hot ninety-five-per-cent. alcohol to saturation, cooling, and filtering. The cover-glasses are stained for five to fifteen seconds. The ordinary bacteria stain feebly or not at all.

The detection of the gonococcus in septicæmic cases can be accomplished by drawing 5–10 c.c. of blood from the vein of the arm and adding this, in about equal parts, to melted agar at 45°. The mixture is at once poured into Petri dishes, and these are developed at 37° C. In this way the gonococcus can be detected when stains would fail to show the organism.

The culture test for the gonococcus is rarely resorted to on account of the difficulty of obtaining the necessary blood or serous fluids. The ordinary media have always been regarded as unfavorable for the growth of this organism. According to Thalmann, Wildbolz, and others, the gonococcus can be grown on ordinary one-and-one-half-per-cent. meat-peptone agar. Thalmann recommends very highly such a medium for diagnostic purposes, and especially where direct microscopic ex-

amination is unsatisfactory or negative. The acidity of ordinary agar or bouillon is reduced by the addition of two-thirds of the amount of alkali necessary to make the media neutral to phenolphthalein. The preparation of these media has been given.

8. *Leprosy*.—The leprosy nodules are characterized by the presence of enormous numbers of the specific bacillus which can be readily detected by staining. The Ziehl-Neelsen method, as employed for the tubercle bacillus, will give excellent results if the tissue is reasonably fresh. When kept for some time in alcohol the bacilli lose their staining properties so far as this method is concerned, but they can still be found by means of Gram's method. Animal inoculations and cultures are not possible.

9. *Cerebrospinal Meningitis*.—The *Diplococcus intracellularis meningitidis* is found in the cerebrospinal fluid. Hence during life it is necessary to remove some of the fluid by lumbar puncture. This fluid should be planted abundantly on glycerin, or better on serum agar. Cover-glass preparations made direct will show the typical organism resembling the gonococcus in form and in its presence within the leucocytes. It is not stained by Gram's method, but can be given a double stain by that of Fick and Jacobsen, or by the modification suggested by Fraenkel. The dye is made by adding to 20 c.c. of water eight drops of a saturated solution of methylene blue, and then forty to fifty drops of carbolic fuchsin. The dye is allowed to act for five minutes. The cocci are blue on a red background.

10. *Pneumonia*.—In all pneumonic conditions the blood-streaked sputum should be examined by making simple and Gram stains. In this way it becomes possible to recognize the pneumonic form of plague. Ordinarily, however, pneumonia is due to the Fraenkel diplococcus and at times to the Friedländer pneumobacillus. The form, staining, and cultural properties of these organisms permit ready differentiation and identification. The lance-shaped diplococcus of Fraenkel, as found in the body, is surrounded by a capsule, and is stained by Gram's method. The colonies and cultures on glycerin agar are very faint and dewdrop like, and tend to die out in a few days. Their vitality and virulence are best preserved by cultivating them on rabbit blood or serum agar. Calcium broth may be used for the same purpose. In doubtful cases the material should be injected under the skin of the ear of a rabbit. If death results the diplococcus will be found in large numbers in the heart blood and organs of the animal.

11. *Rabies*.—The cause of this disease is as yet unknown, but it is to be found, in pure condition so to speak, in the brain and spinal cord of the affected person or animal. The diagnosis rests upon animal inoculation with such material. A few drops of a suspension of the brain or cord are injected subdurally into a rabbit or guinea-pig. The method has been already described.

The histological changes in the nervous system are very slight, and it has been suggested that the diagnosis of rabies may be hastened by making an examination of sections of the cord and ganglia. The lesions are not sufficiently marked in all cases to permit diagnosis, and for that reason this method should not be relied upon to the exclusion of the only positive test, that of animal inoculation.

The recent work of Williams upon "Negri bodies" has called attention to the fact that a rapid diagnosis may be made from smear preparations of the brains from animals suffering from rabies. After a long series of observations, both clinical and experimental, the Department of Health of New York City has adopted this method of diagnosis. Their present method of procedure is as follows: Make smear preparations from the cortex taken from the region corresponding to the fissure of Rolando, Ammon's horn, and the cerebellum. The smears are fixed while moist in a solution composed of methyl alcohol (previously neutralized with sodium carbonate) containing one-tenth of one per cent. of picric acid.

After allowing to act one to two minutes, pour off the fixing fluid, and blot with fine filter paper.

The stain is prepared by adding five drops saturated alcohol solution methylene blue, and one drop saturated alcohol solution basic fuchsin, to 10 c.c. distilled water. This should be freshly prepared just before using. Pour stain on slide; warm until it steams; pour off; rinse smear in water; blot and allow to dry. Upon examination under the oil-immersion lens, the "Negri bodies" will be found in the nerve cells. The cytoplasm of the "bodies" takes a distinctive red color; their inner structures a dark blue. The nerves are light blue, and the blood cells a pale salmon-red. At room temperature this stain is not permanent, but it has the advantage of being a very rapid method for the diagnosis of rabies.

12. *Tetanus*.—The point of inoculation must be found first. This may not always be easy, for the original wound may have healed over. The portal of entry may be a bad tooth, or the wound produced by an old rusty nail, a splinter of wood, or the powder grains of a pistol. Cover-glass preparations should be made from the pus, if there is any; and, if not, from such serum, blood, or tissue as can be obtained from the wound. They should be stained with carbolic fuchsin. The specimen should be examined for "drum sticks" or rods with terminal spores, and particularly for the presence of rather narrow, long bacilli. These are present even when no spores can be found.

Cultures should be made on glucose litmus gelatin, and at the same time a series of glucose agar plates should be made and developed at 37° C., either in hydrogen or in the pyrogallate apparatus. The original tissue should be planted under the skin of a white mouse and of a guinea-pig. The cultures when developed are carefully searched for the drum-stick forms.

13. *Tuberculosis*.—The pulmonary form is usually recognized by an examination of the sputum, preferably that which has been collected in the morning on rising. The cheesy particles, if such can be recognized, should be picked out by means of the wire and spread over the cover-glass. The specimen is then stained by the Ziehl-Neelsen method already given. The red rods on a blue background are readily recognized.

The same method is employed in the examination of pleuritic fluid, pus, urine, milk, etc. In all these examinations, however, two facts should be borne in mind. In the first place the tubercle bacilli may be present, but in such small numbers that they escape detection. Again, acid-resisting organisms, such as the leprosy, smegma, timothy-grass bacillus, etc., may be present, and may be easily mistaken for the tubercle bacillus.

In either case it is the animal experiment which will serve to remove the doubt. When the tubercle bacilli are few or doubtful, it is well to submit the material to preliminary centrifugation. The deposit can be used then for staining and for injection. The injections should be made into the peritoneal cavity of the guinea-pig. If tubercle bacilli are present in the material used, even if so scarce as to be unrecognized by the microscope, the animal will develop the disease and will die in the course of a month or two. The tuberculous organs and glands can be examined then for tubercle bacilli, and cultures can be made on glycerin agar, potatoes, and on Hesse's Heyden agar. The acid-resisting bacilli, other than the tubercle bacillus, are not fatal to animals, and, moreover, the histological changes which they induce are quite different from those caused by the tubercle bacillus.

14. *Typhoid Fever*.—The verification of the diagnosis is usually made by means of the agglutination test of Widal, which will be described later. The direct detection of the typhoid bacillus in faeces, urine, blood, rose spots, and in water presents marked difficulties. The reason for this lies in the very great similarity which exists between the typhoid and the colon bacillus. Numerous methods have been devised for the purpose of effecting a distinction between these two organisms; and while it is an easy matter to differentiate between the

pure cultures of the typical organisms it becomes vastly more difficult under natural conditions, especially when, as often is the case, the para-colon and para-typhoid bacilli are present.

Some of these methods endeavor to restrict the growth of the colon and of adventitious bacteria by the addition of antiseptic substances to the media. Thus carbollic bouillon, Parietti's carbollic hydrochloric-acid broth, malachite-green agar, and crystal violet are used with this object in view, but there can be no doubt that weak typhoid bacilli are also inhibited.

Other methods are based upon the unequal diffusion of the two organisms in special media. The Stoddard, Hiss, and Capaldi media belong to this class. Again, the effort is made to bring out differences between the colonies of the Eberth and colon bacilli, as in the case of the Holz potato gelatin, Elsner, Weil, Hiss, and Piorkowski media. These are all described in the foregoing pages. Still other methods seek to utilize the differences in the fermentative powers of these organisms, as evidenced in the production of gas, acid products, etc. Lastly, there are several methods which have only recently been devised in which the distinction is effected by means of the agglutination reaction. That of Windelbandt, as modified by Schepilewsky, certainly seems to be effective in detecting typhoid bacilli in tap water. Its real value in the examination of typhoid fæces remains to be demonstrated.

Schepilewsky's procedure is as follows: Several cubic centimetres of the infected water are added to 50 c.c. of bouillon in an Erlenmeyer flask, which is then incubated for twenty-four hours at 37° C. The culture is now filtered through a sterile cotton filter in order to remove any compact masses of bacteria which may be present. The filtrate is received in conical centrifugating tubes. A very active serum from a rabbit, which has been immunized to the typhoid bacillus, is then added to the cloudy filtrate, and this is set aside for two to three hours at 37° C. If many typhoid bacilli are present, visible agglutination may be noted; but if they are not abundant, the masses will be so small that agglutination may not be detected. In either case the tubes are centrifugated for one to two minutes, after which the fluid is decanted and the tubes are inverted so as to drain as completely as possible. Sterile sodium-chloride solution is then added to the tubes and the deposit is taken up and transferred to a sterile test tube which contains glass beads. By vigorous shaking, the agglutinated masses can now be broken up and a homogeneous suspension obtained. A glass rod, bent at right angles, is then dipped in the suspension, and streaked thoroughly over the surfaces of a number of plates of the special agar. The latter is a three-per-cent. agar, to which after sterilization in an autoclave a lactose and laemoid solution is added. This consists of 1.5 per cent. lactose and 0.04 per cent. laemoid, and before addition is boiled fifteen minutes. The Petri dishes are developed at 37° C. for twenty-four hours. The typhoid colonies are round or oval and sharp-bordered; later they show the typical spreading form, and the color of the centre changes to a dirty yellow.

The typhoid-like colonies should then be examined under the microscope and submitted to further identification. A suspension of the colony may be tested for the agglutination reaction with typhoid serum. Pfeiffer's reaction may be tested for by injecting a mixture of antityphoid serum and the organism into the peritoneal cavity of a guinea-pig, as described under Cholera. The cultures should also be tested for gas production, indol, milk coagulation, and on the special plating media.

The malachite-green enriching method of Lentz, Endo's fuchsin agar, and MacConkey's bile-salt lactose agar are recommended by different workers for the separation of the typhoid bacillus from fæces.

For the cultivation of the bacillus from patients' blood, perhaps the ox-bile medium of Coleman and Buxton furnishes the best method.

In the absence of the serum necessary for the above

method recourse may be had to the plating medium of Hiss, the urine gelatin of Piorkowski, and the Drigalski-Conradi agar, the preparation of which has been given.

15. A number of infections due to moulds and allied forms and also to yeast-like bodies have been described. The former are represented by the streptothrices, or, more correctly, by the actinomyces of Madura foot and of cattle farcy. The yeast or blastomycotic affections have been noted in certain forms of dermatitis, and may even be systemic in character. In all these diseases the examination of the pus and of sections of tissue, as well as the culture of the organism, must be carried out.

16. *Protozoal Diseases.*—Several very important diseases are due to organisms of this class. The examination for amœbæ in tropical dysentery has already been touched upon. The sporozoa include among others the plasmodium of malaria, the piroplasma of Texas fever, of "spotted fever," and of horses, sheep, and dogs. The flagellata cause the various trypanosomatic diseases, such as the surra of Asia and of the Philippine Islands, nagana or the tsetse-fly disease of South Africa, dourine or "maladie du coit" of the Mediterranean littoral, caderas of South America, the Gambian fever and the sleeping-sickness, the last two being diseases of man. Moreover, many animals harbor in the blood parasites of this group, as in the case of the wild rat.

In all suspicious cases the blood should be examined for these two groups of organisms. The plasmodium of malaria is found especially within the blood cells. The trypanosomes are free in the plasma. The blood may be examined direct under the cover-glass, or in hanging drop, or in a Ranvier slide. Stained preparations can be made with methylene blue, thionin, or best with some modification of the Romanowsky method. The preparation of the specimens and the staining methods have already been described. The trypanosomes of the rat and of nagana, cultivated by Novy and McNeal, are the only pathogenic protozoa which it has been possible to grow artificially. Their presence is best detected by direct examination of the blood, though at times they may be very difficult to find, and may require daily examinations for several weeks.

DETERMINATION OF THE THERMAL DEATH POINT OF BACTERIA.—In this work and also in testing disinfectants it is necessary to have almost homogeneous suspensions of the organism to be tested. Water suspensions should be used first, and later those of bouillon, serum, etc. The liquid is introduced by means of a bulb pipette into the tube of an agar culture. The growth is rubbed up as much as possible, and the suspension is then transferred to a sterile glass-wool filter. In this way the masses of bacteria are removed. The cloudy filtrate may be used as such, or it may be diluted so as to have fewer organisms in the test. It may be used as such for determining the action of moist heat and for testing disinfectants. Again, for dry-heat work and for many disinfecting tests the suspension is allowed to dry upon the surface of sterile glass slips, glass or garnet beads, silk threads, muslin squares, etc.

To test the action of dry heat a number of cover-glasses on which the test organism has been dried are placed in a sterile Petri dish and exposed to a given temperature. At given intervals a specimen is removed and planted in bouillon.

To test the action of moist heat the best procedure is to draw up the liquid into sterile capillaries, as shown in Fig. 5121. The tube is sealed below and above the liquid. The advantage of this method lies in the fact that the heat promptly penetrates every part of the suspension. A number of tubes thus equipped are placed in a water-bath, the temperature of which is kept at a constant point by means of a regulator. At intervals a capillary is removed, cooled, opened at one end, and the contents are expelled into a tube of bouillon by gently touching the closed end to a flame.

Testing of Chemicals.—In this work it is necessary to distinguish between the antiseptic and the disinfecting action of a substance. The former refers to the amount

of the substance which will inhibit the growth, but not necessarily kill the organisms. The latter implies the actual destruction of the test object. Obviously a substance which will kill bacteria, when diluted sufficiently will merely restrict their growth, and when the dilution is excessive will have no action whatever.

The antiseptic action is determined by adding to the suspension in bouillon varying amounts of the chemical

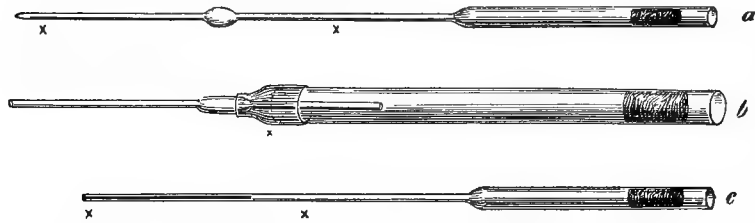


FIG. 5121.—Filling of Capillary Tubes for Thermal Death-point Determinations. c, Tube filled ready to be sealed at x; b, emptying of tube. (Novy.)

so as to make different dilutions, for example: 1 in 500, 1 in 1,000, 1 in 5,000, 1 in 10,000, etc., solutions. The tubes thus equipped are then placed in the incubator for several days. The very weak solutions will show growths, while the very concentrated ones will show none. The amount which just inhibits the growth represents the antiseptic power of the substance.

The germicidal action of a gas, such as formaldehyde, is determined by exposing cover-glass preparations, silk threads, bit of muslin, etc., impregnated with the suspension, dry and moist, to the action of the gas in a tight room. At the end of the exposure the preparations are transferred to sterile tubes of bouillon and inoculated.

The germicidal action of liquids is ascertained, either by adding the solution to the bacterial suspension or by immersing in the solution the dried cover-slip preparations mentioned. In the former case, at stated intervals, a small loop of the liquid is transferred to bouillon, while in the latter case the slip or thread is first rinsed in sterile water and then placed in the bouillon.

The Serum Agglutination Test.—The serum of an animal which has been immunized to a germ when brought into contact with a suspension of that germ will cause the organisms to gather in masses. This fact is utilized in the Widal test for typhoid fever. A drop of the serum from a typhoid patient is diluted with ten, twenty, thirty, fifty, one hundred drops respectively of water in a watch-glass. A drop of each mixture is then transferred to a cover-glass and inoculated with a very small amount of a fresh agar culture of the typhoid bacillus, care being taken to avoid an excess of the organisms. Hanging drops are then made and the preparations examined under the microscope. The limit of the reaction is indicated by the dilution which is just able to cause paralysis of motion and clumping in one hour. Instead of diluting with water some prefer to use a very young bouillon culture. The agglutination test is most delicate when carried out under the microscope. Very good results, visible to the unaided eye, may be obtained by adding the serum to bouillon culture of the organism. The tubes thus treated should be set aside for some hours at 37° C. when the agglutinated masses will settle to the bottom and leave the liquid clear. When applying the test to a suspected case of typhoid fever it is not always possible to obtain large amounts of the serum. In such instances the blood may be placed in single drops on a sheet of filter paper, or, better, tinfoil. The dilutions can then be made with these drops of dried blood as with the serum itself. The application of this test to the recognition of the typhoid bacillus in drinking-water, faeces, etc., has been given.

Preparation of the Soluble Bacterial Toxins.—Soluble or extracellular toxins are produced by a number of pathogenic bacteria (*B. diphtheriae*, *B. tetani*, *B. botulin*, etc.) when grown upon proper culture media, under

favorable conditions. For the purpose of practical immunization of animals, it is necessary to have highly concentrated toxins; therefore, precautions must be taken in cultivating, to bring about the proper conditions. Although the question of toxin production is as yet not fully understood, experience has shown that certain media are more favorable than others, also certain strains of the same organism vary in their ability

to elaborate toxins. In the preparation of diphtheria toxin, Park recommends as a suitable culture medium a nutrient broth prepared in the regular manner from young veal. To each litre add two per cent. peptone (Witte), and sufficient alkali to give an alkalinity equivalent to the addition of 8 c.c. of normal solution of potassium hydrate above the neutral point to litmus. Sufficient nutrient broth is placed in thin layers (about two inches deep) in large-necked Erlenmeyer flasks, to allow free access of air. After inoculation with *B. diphtheriae*,

the flasks are incubated between 35° and 36° C. The greatest concentration of toxin is present between the fifth and eighth days of bacterial growth. After the tenth day, at incubator temperature, the toxicity decreases more or less rapidly, owing to its labile character. After one week's growth, a test for purity of culture is made by microscopical and culture methods. If found pure, the bacteria are killed by the addition of ten per cent. of a five-per-cent. solution of carbolic acid. After standing for forty-eight hours, the dead bacilli settle to the bottom, and most of them may be removed by filtering the broth through ordinary sterile filter paper. Bottles are filled with the so-called toxin, sealed, and stored in ice chest until needed. A hypodermic injection of 0.01 c.c. or even less should kill a 250 gm. guinea-pig.

The bacillus of tetanus also produces a very powerful poison under artificial means of cultivation. Since the bacillus of tetanus is anaerobic in character, its cultivation for toxin production must be varied from that of diphtheria bacillus. Park's method consists in using a nutrient beef broth of slight alkalinity, containing one per cent. peptone (Witte), 0.5 per cent. common salt, and one per cent. glucose. The broth thus prepared is placed in flasks until they are about two-thirds filled, then sufficient molten paraffin (melting-point about 45° C.) is added to form a semi-solid covering one-half to one inch in thickness. The whole is sterilized and when ready for use the flask is sufficiently heated to liquefy the paraffin layer. A shake culture of *B. tetani* in agar is dropped in the warm medium. The heated broth will cause the agar to dissolve and liberate the organisms and spores. When cool the paraffin hardens over the broth and seals it off from the air, thus producing anaerobic conditions. The agar shake culture is best removed from the test tube by quickly heating until the agar about the wall dissolves; then it may be poured into a flask. Precaution should be exercised to prevent outside contaminations. Allow the culture to grow at a temperature of 37° C. for five to six days. After the necessary tests for bacterial purity are made, the living organisms and spores are removed by first filtering through paper pulp (funnel and suction), then through a Berkefeld filter. To the filtered toxin 0.5 per cent. carbolic acid is added; flasks are then completely filled, sealed, and kept in a cool dark place. The strength of this toxin is quite variable, much depending upon the conditions of preparation. According to Park, under best conditions, the amount of toxin produced in cultures on the fifth day may be such that 0.000005 c.c. is a fatal dose for a 15-gm. mouse. Tetanus toxins as prepared by the above method may show such a degree of toxicity that 0.001 to 0.0001 c.c. will cause death within four days to a guinea-pig weighing from 300 to 350 gm.

These two toxins indirectly have an important bearing upon practical medicine. They are used to immunize horses in the preparation of specific antitoxins. The other soluble bacterial toxins may be prepared in a similar manner, but the composition of media and conditions must be altered to meet the special requirements of the organism under cultivation.

Methods of Immunization.—Only the general principles of active immunization can be considered. The injections are made subcutaneously, intraperitoneally, and intravenously. When immunizing a horse for the production of antitoxin serum, the injection of toxin should always be made subcutaneously. Experience has proved that the antitoxin is formed much more rapidly, and reaches a higher concentration in the blood under such procedure. The primary dose of toxin for a normal animal must be very small. An initial dose of 0.01 c.c. of diphtheria toxin has proved fatal to a horse. Therefore, in immunizing a previously untreated horse, it is necessary to begin the injections of diphtheria toxin (also tetanus toxin) with a dose under one-hundredth of a cubic centimetre, to keep within bounds of safety. A repeated injection of toxin should not be given until the animal has practically recovered from the reactionary symptoms of the previous dose. In the routine immunization of horses against diphtheria Park recommends that the initial dose be about 20 c.c. of fairly strong toxin; the second and third doses are slightly increased. But with each of these injections about 10,000 units of the antitoxin is given. In this way the animal is protected until it has an opportunity to elaborate its own antibodies, then the injections of antitoxin may be discontinued. This procedure aids in bringing an animal without danger up to a high degree of immunity in a relatively short time, as compared with the older method. In either case, after a few months' treatment, a horse may withstand several hundred cubic centimetres of highly potent toxin, at a single injection, without serious results. When a soluble poison is injected, a true antitoxin develops in the animal and is present in the blood and hence in the serum. This is the case in diphtheria, tetanus, and venom immunity. On the other hand, when the solid cell is injected, the serum may acquire anti-infectious properties, the best instance of which is seen in the anti-pest serum. The organisms may be killed by exposing them to the action of ether, of chloroform, or of moist heat at 60° C. In special cases the attenuated living germ is used, and at times even the most virulent form is employed. By the injection of cells other than bacteria, diverse cytolytic sera are obtained. Thus the injection of the red blood cells gives rise to a hæmolytic serum. The temperature and the weight of the animal must be taken daily, since they afford the best indication of the condition of the animal.

Testing the Strength of Antitoxin.—The strength of an antitoxin is expressed in immunity units. A unit represents that amount of serum which will be just sufficient to protect a 250-gm. guinea-pig against 100 minimum fatal doses of the diphtheria toxin. Thus if 0.1 c.c. of serum protects against this dose of poison, then it will contain 1 immunity unit, and 1 c.c. of such serum will contain 10 immunity units. It is possible to prepare diphtheria antitoxin of such strength that 1 c.c. will contain more than 1,000 immunity units. Usually, however, the serum as marketed contains about 200 immunity units per cubic centimetre.

Gibson, working under the directions of Park, succeeded in preparing a concentrated preparation of diphtheria antitoxin by precipitating the globulins from antitoxic serum by the addition of certain salts. The globulin precipitate which contains the antibodies is purified by redissolving and precipitating several times. The salts are finally removed by dialysis. By this method a preparation may be obtained which contains 1,500 to 1,800 units per cubic centimetre. These so-called antidiphtheritic globulins or concentrated anti-

toxins are now prepared by different serum laboratories.

The first essential is to ascertain the minimum fatal dose of the toxin, by which is meant the amount of toxin which will kill a 250-gm. guinea-pig on the fourth or at most on the fifth day. The toxin itself as described is a bouillon culture of the diphtheria bacillus, which has been rendered sterile by the addition of a small amount of carbolic acid.

Varying amounts of the serum are then added to portions of the toxin representing one hundred minimum fatal doses. These mixtures are then injected into guinea-pigs of the weight given. That fraction of a cubic centimetre of the serum which just suffices to save a guinea-pig under these conditions represents, as stated above, one immunity unit.

This method is subject to some error, inasmuch as it has been found that a serum which has been tested against one toxin will show a different value when tested against another. This is due to the fact that the toxin undergoes changes on keeping, and is converted into a non-poisonous body or toxoid, which, however, retains the power of combining with the antitoxin. For this reason Ehrlich proposed a new method of testing the antitoxic value of a serum. A standard dried antitoxin is made the basis of the measurement. This is diluted so that a given amount just represents one immunity unit. The test dose of toxin is then ascertained and represents the amount of toxin which, mixed with one immunity unit of serum, will cause death on about the fourth day. The serum to be tested is then diluted, mixed with the test dose of the toxin, and injected into a guinea-pig. If the animal dies in a day or two it is evident that the serum contains less than one immunity unit. If, on the other hand, it lives for seven or eight days, or even recovers, it shows that the amount of serum taken contains more than one unit. By using suitable dilutions of the serum, eventually the point will be reached where the amount taken will represent exactly one unit.

OPSONIC TECHNIQUE.—The fact that certain cells of the body will take up and destroy microorganisms has been known for years. The phagocytic theory of immunity is based upon this phenomenon. Denys and Leclef were the first to demonstrate the presence of a substance in immune serum which made the corresponding organism sensitive to phagocytosis. They showed that this substance acted upon the organism and not on the leucocytes. More recently Wright and Douglas have called attention to the fact that such sensitizing substances are present in fairly constant amounts in the normal blood. This substance, which they call opsonin, exists in much lesser amounts or widely fluctuating amounts in the blood of a patient suffering from specific bacterial infection. The opsonic content may be increased by properly vaccinating with killed cultures of the specific organism. Bacterial vaccines are now coming to play an important rôle in the newer therapeutics. It is obvious that such means of treatment must be carefully controlled, or, instead of being of material aid to the body, they become a damaging factor. Therefore, in order to follow opsonic treatment, a means must be found by which a fairly accurate measurement can be made of the opsonins in normal bloods and in the bloods of patients suffering from any bacterial infection. Wright and Douglas have practically overcome this difficulty by a technical method by which they derive the so-called "opsonic index." This "index" simply shows the relation existing between the opsonic content of a patient's blood as compared with the opsonic content of the blood of a normal person.

The general method used in deriving the opsonic index calls for the following materials: Blood serum from patient; control serum from normal person; normal washed corpuscles, and the bacterial emulsion.

The same technique is used in preparing serum from both the patient's and normal blood. A puncture is made in the lobe of the ear or one of the fingers with a

needle, and pressure is used to cause the blood to flow. When the blood begins to exude, eight or ten drops are drawn up into a pipette, and at once transferred to a small test tube, about one-quarter inch in diameter and two inches in length. The blood is allowed to clot, thus permitting the serum to separate.

To secure the leucocytes, the blood is drawn from the patient directly into a small test tube containing about 5 c.c. of a one-and-one-half per cent. solution of sodium citrate. This solution prevents the blood from clotting. One cubic centimetre of blood will furnish a sufficient number of leucocytes for the test. The corpuscles are centrifuged until the solution above the packed cells appears transparent. Carefully remove the solution with a capillary pipette, then add about 10 c.c. of physiological salt solution, and shake well to wash the cells. Centrifuge again to throw down the corpuscles, and remove the salt solution with capillary pipette. Be careful not to disturb the superficial creamy layer of blood cells, as this layer contains the greater share of the leucocytes. When the fluid has been removed, take up the leucocyte layer of cells carefully with a capillary pipette, and reserve the thick emulsion for the test. Blood which shows any clotting must be rejected.

The bacterial emulsion should be a uniform suspension, but it is very difficult to avoid some clumping of organisms. Different organisms vary in this respect. Tubercle bacilli are extremely hard to get into a uniform suspension. To prepare an emulsion of such organisms as staphylococci, streptococci, pneumococci, and such bacilli as typhoid and colon, cultures are grown on the most favorable agar medium, and used fresh, *i.e.*, not older than twenty-four hours. Remove a portion of the culture with a medium-sized platinum wire, and transfer to a small test tube containing 3 or 4 c.c. of physiological salt solution. With the wire, carefully rub the mass of organisms against the wall at the surface of the salt solution until a turbid suspension results. Centrifuge until the larger particles of bacteria are thrown down, but discontinue before the finer suspension is sedimented. Experience will indicate the proper degree of turbidity which is desirable. Wright recommends that the bacterial suspension be such that four to five cocci are found for each cell in the final mixture.

For emulsion of tubercle bacilli some workers cultivate the organism on glycerin agar and kill the organisms by exposure to direct sunlight for twenty-four hours, or by other means. Some of the growth is removed from the culture tube, and placed in a small agate mortar, where it is thoroughly rubbed up with 1.5 per cent. salt solution. The resulting suspension is centrifuged to remove clumps. Other workers prepare their emulsion of tubercle bacilli from dried and ground-up bacilli. In preparing the emulsion, the procedure is the same as the above. In each case when the emulsion is finished, remove upper portion from the centrifuge tube, with a pipette, and reserve for use. Wright states that the tubercle emulsion should be of such thickness that one or two organisms are found to each cell in the final smear.

Now, having prepared the necessary materials for the work, the next step is to measure out the blood cells, serum, and bacterial emulsion for mixtures. Best for this purpose is a pipette made by taking glass tubing with about 5 mm. internal diameter and about 15 cm. in length. Draw out in flame in the same manner as described under Pasteur pipettes (Fig. 5096, b), with the exception that no end constriction is made. The capillary portion of each should be about 12-15 cm. long and about 1 mm. in diameter. A rubber nipple, such as is used on an ordinary medicine dropper, is slipped over the large end. The capillary end is cut off squarely and a mark is made with a glass marking pencil about 3-4 cm. from the end. By means of the nipple, fluid can easily be drawn up into the capillary tube. The mixture is made by drawing up the heavy suspension of blood corpuscles (containing leucocytes) to the

pencil mark; a little air is drawn in by raising the blood column, then draw in an equal volume of serum by filling up to the pencil mark; again allow an air bubble to enter; then finally draw in an equal volume of the bacterial suspension. In this way the different suspensions can be equally and accurately measured. The whole content is blown out of the pipette on a clean, hollow-ground slide, where it is thoroughly mixed by drawing up and ejecting from the pipette several times. Finally, the whole mixture kept free from air bubbles is drawn up into the pipette and the capillary end is sealed off in a flame. Place the pipette containing the mixture in an incubator at 37° C. for fifteen minutes to permit phagocytic action to take place. After removing from the incubator the sealed tip of the pipette is broken off, and the suspension is well mixed on a clean hollow-ground slide. Drops of moderate size are placed upon each of a number of clean slides. Spread each drop by means of the end of a second slide, as is done in ordinary blood work. Allow the smear to air-dry completely, then stain with aqueous methylene-blue solution, or with a polychrome dye such as the Wright or Leishman stain. In the case of tubercle bacilli the films are fixed in saturated aqueous solution of mercuric chloride ten minutes. Wash in water, stain with Czaplewsky's carbol-fuchsin solution, and again wash in water. Decolorize in two-per-cent. sulphuric acid, wash well, and counter-stain one minute with one-per-cent. aqueous solution methylene blue. Dry the stained preparations and examine under high-power objective. The bacillary index is found by taking the total number of bacteria counted in a series, and dividing it by the number of leucocytes making up the series. Fifty or more leucocytes should make a series. The opsonic index is derived by dividing the value (bacillary index) of the patient's serum by the value found for the normal serum used as control. It is an advantage to collect the normal serum from three or four healthy persons and mix all together. This gives more reliable results in finding the opsonic value for the normal condition.

In making counts for the opsonic index, the personal equation is frequently pronounced, but by continued experience this factor may become lessened and fairly constant. It also must be noted that marked discrepancies exist between results of experienced workers when estimating the opsonic index of the same sample of serum. Simon recommends that the percentage of phagocytizing leucocytes be estimated in connection with the bacillary index. He states that this will act as a check upon the bacillary index, and will reveal errors in counting. A close correspondence exists between the bacillary index (Wright) and the percentage index of Simon.

Examination of Air.—The bacteria which chance to be present in the air are in a dried condition, and tend to settle when the motion of the air is lessened. The simplest method consists in exposing a plate of gelatin or agar to the air for a given length of time. Some of the organisms settle on the gelatin and eventually give rise to colonies. Koch improved slightly upon this by placing the gelatin plate in the bottom of a sterile cylinder of known volume. After opening the cylinder in a given locality it is closed with a cotton plug and set aside, when the organisms contained in that volume of confined air settle to the bottom on the surface of the plate. The results, it will be seen, are crudely quantitative (Fig. 5122).

Hesse's method consists in drawing the air through a large Esmarch roll tube (Fig. 5123). The volume of the air drawn through can be determined from that of the aspirating bottles. The bacteria in the air impinge upon the gelatin surface, where they develop into colonies which can be counted and studied.

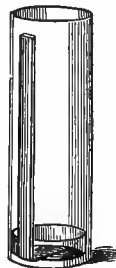


FIG. 5122.—Koch's Cylinder for Air Analysis.

The apparatus of Petri, although very expensive, may be said to give the best results. It consists in the first place of an air pump, which automatically registers the movements of the piston, and thus gives the volume of the air which has been drawn through. The air is aspirated through a tube (Fig. 5124) containing several



FIG. 5123.—Hesse's Apparatus for Air Analysis.

layers of sterile sand. The suspended bacteria are thus held back. At the close of the operation the sand is transferred to a Petri plate, where the bacteria will form colonies and thus become accessible for study.

Instead of sand, Sedgwick and Tucker employed a filter of sugar. The special tube employed by them is shown in Fig. 5125. After the air has been drawn through, the sugar is tapped down into the wide portion of the tube, then gelatin is added and warmed until the sugar dissolves, after which an Esmarch roll culture is made in the same tube.

Other workers have filtered the air through liquid media or through gelatin. The most convenient form of apparatus of this kind is that of Wurtz, shown in Fig. 5126. A suitable amount of gelatin is placed in the sterile tube, then a known volume of air is drawn through, after which the gelatin is solidified over the inner wall of the tube, thus forming a roll culture.

Examination of Soil.—By means of a small sterile platinum spoon a definite volume of the soil may be transferred to a Petri plate, where it is thoroughly mixed with the medium. The colonies which develop can then be examined. In this way it is possible at times to demonstrate the presence of the anthrax bacillus in the soil of an infected locality. The detection of other pathogenic bacteria, as for instance those of tetanus and malignant cedema, can best be made by introducing a quantity of the soil under the skin of a guinea-pig or rabbit.

Examination of Water.—This is a very important procedure, and an enormous amount of work has been done to perfect the methods of work. The method followed

will necessarily depend upon the immediate object in view. Thus the detection of the cholera vibrio is carried out in a different way from that used for the colon bacillus. The isolation of the cholera and typhoid organisms from water has already been described.

The water which is to be tested bacteriologically must be received into a sterile glass-stoppered bottle, and should be examined at once. The first step in the examination is to make gelatin plates. By means of a sterile pipette 1 c.c. of water is added to a tube of gelatin, mixed thoroughly, and the gelatin is then poured out into a Petri plate. In the same way plates are made with 0.5 c.c. and with one drop of the water. The gelatin plates are developed at 20° C. for several days. The colonies are then counted and examined in the usual way. When only a few colonies are present on a plate they can be readily counted with the eye. When the number is large special counters are made use of. That of Wolffhügel (Fig. 5127) is ruled in squares of 1 cm. and fractions thereof. Another form is that of Lafar. A very useful and cheap substitute is made by printing the divided circle on card paper. To make a count, the number of colonies in ten or more squares is ascertained, and the average per square centimetre is obtained. The area of the gelatin on the plate is taken and then the total number of colonies on the plate determined, and the result is expressed per cubic centimetre of water.

Instead of using Petri plates, the Esmarch roll tube can be made. To count the colonies in such a tube Esmarch devised the counter shown in Fig. 5128.

When the number of colonies is likely to be extremely large, as in the examination of polluted water, it is advisable to dilute a portion of the sample with a known volume of sterile water. If the colonies are very numerous on a plate, the counting can be carried out best under a microscope. Ehrlich stops are placed in the eye-piece or the special Ehrlich ocular may be used. The size of the opening in the ocular must be determined by means of a stage micrometer. The average number of colonies for a given-sized opening is determined,

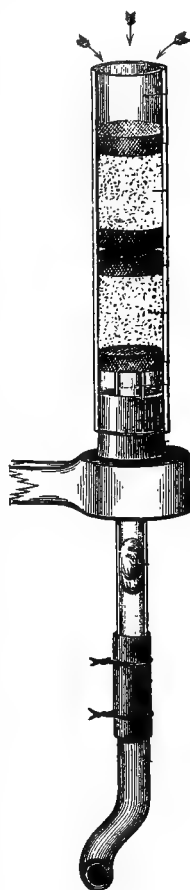


FIG. 5124.—Petri's Sand Filter for Air Analysis.

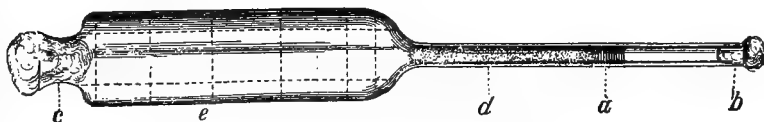


FIG. 5125.—Sedgwick and Tucker's Aërobioscope.

and from this the total number on the plate is calculated.

The above method of examination gives approximately the number of bacteria which are present in a water, and to some extent information as to the kind of bacteria. It is of great value, therefore, in controlling

the work done by the water filters. In order to ascertain the presence of pathogenic and other bacteria special methods must be resorted to. The method which has been employed during the past fifteen years in the Hygienic Laboratory of the University of Michigan consists in planting a cubic centimetre and a drop of the water in tubes of bouillon, which are then incubated at 39° C. If no growth forms, as often is the case, pathogenic bacteria may be said to be excluded. When a growth does form, a portion (1 c.c.) is injected into a guinea-pig. In case the animal dies the heart blood is examined for the kind of organism present. If no ill effects follow the injection, the water may be said to be free from pathogenic bacteria.

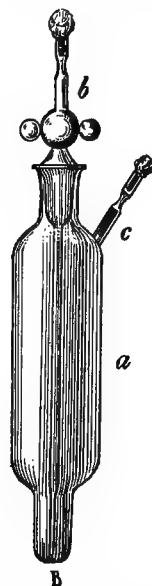


FIG. 5126.—Wurtz's Apparatus for Air Analysis.

Sewage contamination is usually indicated by the presence of colon bacilli and of streptococci. The presence of the former is tested for by means of the Smith fermentation tube (Fig. 5129); 1 c.c. of the water is added to glucose bouillon in the fermentation tube, which is then set aside at 37° C. The formation of gas indicates the probable presence of the colon bacillus, while the non-production of gas points to the absence of this organism. Further tests are necessary for identification.

Litmus-lactose agar plates should be made directly from the water and also from the fermentation tube when gas production is present. The formation of red colonies is indicative of the colon bacillus, since this

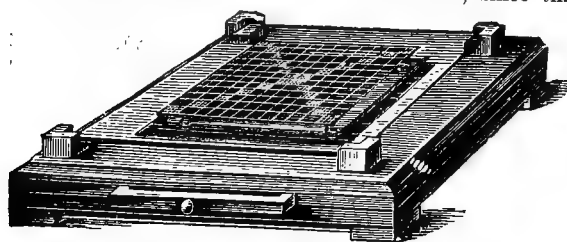


FIG. 5127.—Wolffhügel's Colony Counter.

organism ferments lactose, whereas typhoid-like bacteria do not. For the same purpose lactose bouillon is sometimes employed in the fermentation tube.

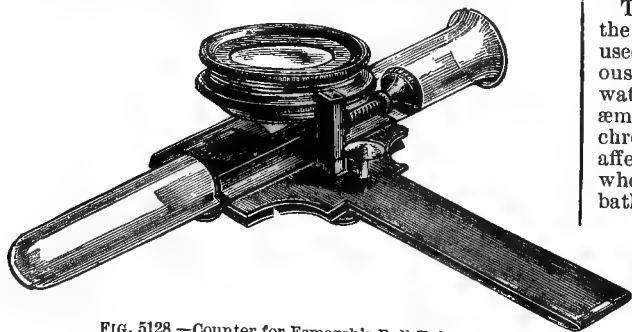


FIG. 5128.—Counter for Esmarch's Roll-Tube Cultures.

Another procedure is to plant the water in carbolie bouillon, or in Parietti's solution, in order to eliminate many of the more common bacteria.

Neutral red bouillon and agar are also used for cultivating the suspected colon bacillus. The water may be planted direct, or the red colonies which form on the



FIG. 5129.—Smith's Fermentation Tube.

plate may be used for inoculation. The coagulation of milk and the production of the indol reaction are additional tests of identification.

F. G. Novy.

Revised by L. W. Famulener.

BADEN-BADEN AND THE BLACK FOREST, GERMANY.

—The region of the Black Forest (Schwarzwald) lying to the east of the Rhine, between Karlsruhe and Basel (Switzerland), is a thickly wooded mountain range of great beauty and picturesqueness, containing many climatic and mineral-water health resorts. The most of these resorts have only a summer season extending from about the middle of May to the end of September; but the open-air cures for pulmonary tuberculosis remain open the whole year, and the winter season is just as efficacious in the treatment of this disease as are the milder seasons of the year. The climate in general is that of Central Europe, with the addition of the peculiar influence of the mountains and the thick fir forests. The elevations of the climatic resorts are from one to two thousand feet. In this country comparable resorts are such places as Rutland, Mass., Saranac in the Adirondacks, and Liberty, N. Y.

Baden-Baden (650 feet) lies at the entrance of the Black Forest from the north, six miles from the Rhine, and is beautifully situated; it is surrounded by hills thickly wooded with the dark fir. It is one of the most popular spas of Europe, and, besides its permanent population of 15,000, it is visited in the summer by about 60,000 people. Moreover, the environs of Baden are most charming, and one can either begin or end a tour of the Black Forest at this point.

The average temperature of the year is 48.3° F., and for the summer as follows: May, 53.9° F.; June, 60.2° F.; July, 62.9° F.; August, 62.2° F.; September, 56.6° F. For the autumn, 47.6° F.; winter, 34.3° F. The yearly rainfall is quite large. The surrounding hills afford shelter from the cold winds in winter, but in mid-summer they prevent the cool breezes from mitigating the heat which, for some persons, is too great for comfort.

The waters contain sixteen grains of common salt to the pint, at a temperature of 110° to 154° F. They are used for drinking, but chiefly for bathing, and in various forms of douches. The maladies for which such waters are recommended are rheumatism, gout, lithæmia, gastric catarrh, catarrh of the bladder, scrofula, chronic metal poisoning, obesity, and chronic catarrhal affections of the respiratory tract. The effect of the waters when drunk is diaphoretic, diuretic, and laxative. The bath establishments are extensive and well appointed, some of them luxuriously so, and include hot-air, vapor, pine, electric, and mud baths, and swimming pools. There is also an inhalation establishment, and a section for Swedish massage and mechanical gymnastics. There is an elaborate and extensive *Conversations-Haus* with pleasant grounds, and near at hand is a *Drink-halle*, most frequented in the early morning, when the waters are drunk to the accompaniment of music, the usual custom in European spas. There are also several private sanatoria under competent direction. The

sanitary condition of the city is satisfactory, and the water supply for domestic purposes comes from mountain wells. The accommodations are abundant, excellent, and of varying price. The baths are open all the year, although they are most frequented during the season (May to October). There are also milk, herb, and grape cures. The situation of Baden with its hills affords opportunity for the "Terrain-Cur." One can also make an "after-cure" here after a course of more active mineral waters.

East of Baden-Baden, in the northeastern part of the Black Forest, is Wildbad (1,410 feet), a much-frequented spa, containing indifferent thermal waters, of a temperature of 91.3° to 104.5° F., used very largely for bathing, although they are also used for drinking and gargling. The town, of about 3,000 inhabitants, lies in the narrow wild valley of the Enz, surrounded by hills covered with pines, and possesses an agreeable climate and excellent drinking-water. The mean yearly temperature is 46.5° F., and the mean monthly temperatures for the season are: May, 53.7° F.; June, 60.8° F.; July, 63.1° F.; August, 62.6° F.; September, 55.9° F. The waters are beneficial for the class of cases for which simple hot baths are appropriate, such as chronic rheumatism, gout, chronic joint pains, metal poisoning, scrofula, functional nervous affections, catarrh of the respiratory organs, nervous dyspepsia, convalescence from acute and chronic diseases, certain gynecological affections, and chronic skin eruptions. The bracing mountain air found here also enhances the value of a visit to this resort. The application of the waters is chiefly in bathing, and they are conducted from the wells in a continual stream at their natural temperature. There are also electric, steam, and hot-air baths; massage and gymnastics. There are several bath establishments, the property of the Government, two excellent ones, the Great Bathhouse and the König Karls Bad, and others for the poor or those of slender means. There are a variety of outdoor amusements, such as fishing, shooting, and tennis; and, as in almost all these resorts so largely visited by English and Americans, an English church.

Not far from Wildbad is Schömburg (2,130), where is situated a sanatorium for pulmonary tuberculosis conducted by a physician formerly attached to the Falkenstein Sanatorium, and in a similar manner.

St. Blasien (2,530 feet), in the southeastern part of the Black Forest, has an excellent climate and situation, affording mountain and forest air, and is resorted to both in summer and in winter. There are pleasant walks among the forests in the neighborhood, and the paths are arranged for the "Terrain-Cur." There is a well-known sanatorium here, open the whole year for the open-air treatment of pulmonary tuberculosis.

At Nordrach (1,470 feet), near the centre of the Black Forest, is Dr. Walther's celebrated "Nordrach-Colonie," in a protected position, looking toward the south. The success of Dr. Walther in the treatment of pulmonary tuberculosis has given this place and name a world-wide fame; with the English, especially, this sanatorium is very popular, and the sanatoria, now so frequently being established in England, follow Dr. Walther's methods, and sometimes take the name "Nordrach."

The climate at all these open-air resorts in the Black Forest is practically the same: the air is fresh and pure, fairly dry and equable, and although cold in winter (mean winter temperature, 29.6° F.) it is sunny and there is protection from the wind. The mountain influence is also apparent, and the thickly wooded character of the country is not without value.

Badenweiler (1,450 feet), in the lower part of the Black Forest, is a popular summer resort and spa, and possesses great beauty of situation and an excellent climate, pure air with a moderate humidity of seventy per cent., and an equable, mild temperature. The mean average monthly temperatures are: May, 53.8° F.; June, 61.5° F.; July, 64.6° F.; August, 62.8° F.; September, 57.4° F. The yearly rainfall is about forty inches. Badenweiler is used much more for a climatic health resort than for its

waters, which are indifferent thermal (of 84° F.). They are used in drinking, in gargling, and in baths; and for various maladies—gout, rheumatism, neurasthenia, chronic neuralgia, diseases of the skin, catarrh of the respiratory passages, dyspepsia, dysmenorrhœa, etc. There are two public bathing pools, the "beautiful marble bath," an open swimming pool, and bath-rooms in a number of hotels. The baths are sometimes artificially heated, and common salt is added to render them more stimulating. The milk and whey cures can also be taken here. The sanitary conditions of the town and the water supply are good. There is also a steam disinfecting apparatus. The accommodations are good in hotels and pensions. In the vicinity of Badenweiler are various resorts of different elevations which offer favorable climatic conditions.

Rippoldsau (1,856 feet) is situated in about the centre of the Black Forest near the Kniebis Mountains, in a thickly wooded valley, with typical forest scenery, rocky precipices, cascades, and the ever-present fir trees. The waters are gaseous chalybeate, containing bicarbonate of iron, sulphate of sodium, carbonate of calcium, and free carbonic acid gas. The waters are taken internally in anæmia, chlorosis, debility, dyspepsia, catarrhal conditions of the stomach and bowels, etc. Iron baths are also used from two springs containing a small amount of iron and rich in carbonic acid gas. Mud baths are used extensively here, and are said to be effective in chronic rheumatic swellings, various sexual disturbances such as amenorrhœa, spermatorrhœa, and impotence. There are also pine-needle, electric, and sand baths, with massage and gymnastics. The baths are heated by Schwarz's method, which consists of the introduction of steam into the double bottoms of the separate baths. There are two well-appointed bathhouses containing twenty-five bath-rooms. The yearly average is about thirty-five hundred baths. The water from some of the springs, viz., Josef's, Leopold's, and Wenzel's, are bottled and largely exported, as is also the salt (Rippoldsau salts). The accommodations are good. The rural simplicity of the place remains, many of the old-time costumes being still worn by the natives.

There are numerous other small spas and climatic resorts in the Black Forest, all attractively situated and affording opportunities for hydrotherapeutic treatment or open-air life in a fresh invigorating atmosphere. Indeed, a walking, bicycle, or automobile tour through this most picturesque region may well be considered a cure in itself for tired nerves and the mentally overworked; and the writer, from personal experience, can bear witness to the charm and restfulness of such an excursion: the air is so fresh and invigorating, the food so good, the country scenery so attractive, and the singing of the skylarks so sweet and seductive.

Edward O. Otis.

BAGNÈRES-DE-BIGORRE.—Bagnères-de-Bigorre is a town of about 12,000 inhabitants, attractively situated in the Hautes-Pyrénées, in the extreme southern portion of France, not far from the Spanish border. The town lies in the foothills of the Pyrénées at an elevation of 1,800 feet. The surrounding country is very beautiful and affords many opportunities for pleasant excursions.

The climate is mild and bracing without sudden changes; the atmosphere is clear and pure, partaking more or less of the characteristics of elevated regions; periodic winds traverse the valley, tempering the heat of the warmest days. The mean annual average temperature is 46.5° F., and there are 147 rainy days in the year. The regular season extends from June 1st to October 1st, although the place is frequented both winter and summer by the residents of Pau—a health resort in the vicinity—for the purpose of escaping the heat in summer, and enjoying the clear, dry, bright, and slightly frosty days of winter.

The town is picturesque, with a Spanish appearance, clean and cheerful, with a casino, music, shops, an Eng-

lish church, many delightful excursions, and interesting Roman remains. It is a good place for a long or short stay. The accommodations are good and reasonable.

There are three classes of waters obtained and used at this spa: A. Sulphate-of-lime springs with a trace of arsenic; B. sulphur waters; C. cold ferruginous waters. The sulphate-of-lime springs are the characteristic waters of the place and are of a temperature varying from 88° to 122° F. They are used both internally, and externally in the form of baths, douches, massage, inhalation, vapor baths, etc. There are a large number of hot sulphate-of-lime springs; the Source Salies is the hottest and is without sulphur. The water in appearance is clear, odorless, and of an insipid taste. The direct effect of the waters when taken internally is to stimulate the appetite and digestion, increase the excretion of urine, and render more active intestinal and bronchial secretions. The baths are sedative and soothing to the nervous system; render the circulation fuller and more steady, and the respiration more easy.

The maladies for which these waters are principally employed are those connected with the nervous system, such as hysteria, neurasthenia, insomnia, cases of overwork, chorea, neuralgia and anæmia, chlorosis, gastrointestinal, cutaneous, and arthritic disturbances depending upon a neurotic cause; catarrhal conditions of the respiratory passages; and uterine troubles. "The dominant indication at Bagnères-de-Bigorre," says Burney Yeo, "is neurasthenia."

The contraindications are acute febrile affections and arteriosclerosis in elderly persons.

There are two bath establishments with all the appliances for the various kinds of baths.

Considering the beauty of the situation, the excellent climate, the charm of the town, and the effects of the waters, one could hardly imagine a more favorable resort for a neurasthenic, or one afflicted with insomnia.

Edward O. Otis.

BLACKWATER FEVER.—*Synonyms.*—Hæmoglobinuric malarial fever, Bilious hæmoglobinuric fever, Malarial hæmoglobinuria.

Definition.—A disease or form of disease associated with malarial infection, caused possibly by an invasion of some special form or forms of malarial parasites, and characterized by fever, jaundice, and hæmoglobinuria.

Geographical Distribution.—The disease was first described early in the nineteenth century by French naval surgeons stationed at Nossibé, an island off the northwest coast of Madagascar. It is prevalent in the flat coast regions of tropical Africa, especially on the Gold Coast and in the Congo basin, and is said to be increasing in these regions of late years. It is encountered in Southern China, in some districts of India, in Siam and the East Indies, and in Asia Minor. Cases are occasionally seen in Greece, Italy, and Spain. The disease is not unknown in the Southern United States. It is not uncommon in the West Indies; and on the Isthmus of Panama it causes a considerable number of deaths every year. Hæmoglobinuric fever is found only in regions where malaria is exceedingly prevalent in its severer forms. And it is not found in all of such regions. For instance, malarial fever prevails throughout India; but only in certain notorious districts in Assam, Upper Burmah, and the Terai is blackwater fever encountered. In other regions of India it is practically unknown. The same is true of British Guiana. Laveran never saw blackwater fever in Algeria.

Etiology.—It is quite generally accepted now that blackwater fever is a form of malaria. It occurs only in malarial regions; and if examination of the blood has been made in time, competent observers have been able to demonstrate malarial parasites in nearly every case, though their specific characters were not always determined. Thus, in blood examinations made on the day preceding the hæmoglobinuric attack, Stephens and Christophers¹ and Mannaberg² have found parasites, either estivo-autumnal, tertian, quartan, or of undeter-

mined character, in 95 per cent. of cases. F. Plehn found parasites in 16 out of 19 cases examined on the first day of the disease, in 2 out of 9 cases examined on the second day, and in none of 6 cases examined after the second day. Very early in the attack the disintegration of the infected corpuscles deprives the parasites of their corpuscular hosts and they perish in the plasma.

All races are susceptible to the disease. Europeans are most susceptible, negroes least so. The European sojourner is seldom attacked during his first six months, and Crosse states that a first attack is rarely experienced after three years of residence. Children are seldom attacked, and women less frequently than men. After a prolonged residence in a tropical place where malaria and blackwater fever are prevalent and where the patient has suffered attacks of malaria in its ordinary forms, removal or return to a cold climate often results in an attack of blackwater fever. Bodily exertion, injuries, excesses, and all weakening influences predispose to attack as is the case with other diseases. Individual susceptibility probably varies. One attack predisposes to recurring attacks which almost invariably follow and one of which is likely to be fatal. Fisch has seen permanent recovery after ten or more attacks and believes that after the fourth attack there is a diminishing danger of fatal result.

The administration of quinine, even in small dosage, has sometimes acted as the immediate exciting cause of the hæmoglobinuric symptom.

Pathology.—The gross pathology of the disease is the pathology of malaria. The very extensive and rapid destruction of red corpuscles in the attack is the dominant feature of blackwater fever, and is thus explained by Scheube:³ "In certain particularly notorious fever regions a constant destruction of red blood corpuscles takes place under the influence of chronic malarial infection. In consequence of the continued and unusual demands which are made on the blood-forming organs these no longer grow, so that they partly yield a product weakened in its capacity for resistance. A new invasion of parasites suffices—even of the otherwise benign tertian parasites—with the virus formed by them alone, or in conjunction with another poison introduced in the system, namely, quinine (exceptionally the latter alone), to cause a wholesale destruction of red blood corpuscles, infected and non-infected, and thus to originate blackwater fever. A. Plehn explains that as, in this process of disease, the least valuable blood corpuscles perish, a large dose of quinine can be borne a few days later without exercising a deleterious influence. In this enormous destruction of red blood corpuscles the danger of blackwater fever consists. The hæmoglobin released in great quantities is partly taken up by the kidneys and secreted with the urine, and partly invades the circulation of the portal vein and becomes transformed into biliary pigment in the liver. The result is a superfluous production of bile. As the liver is unable to excrete this completely, a portion finds its way through the lymphatic vessels into the blood, and in this manner icterus is originated (Senator's cythæmolytic icterus). Hæmoglobinuria and icterus are, therefore, the principal features of blackwater fever."

Examination of the blood reveals poikilocytosis, with macrocytes and microcytes. Sambon has observed an absolute leucocytosis in some cases. Pigment granules are absent. The plasma is stained with hæmoglobin in solution. The appearance of nucleated red cells is a sign of commencing regeneration. The hæmoglobin falls rapidly, a hæmoglobinuric attack frequently causing a loss of one-third of the existing percentage, even though that were already low. In a case of Brem's⁴ the hæmoglobin fell from 42 to 28 per cent. in twenty-four hours, and continued to fall till it reached 17 per cent. The loss of hæmoglobin is apt to continue for a day or two after the cessation of hæmoglobinuria. Owing to the fact that corpuscular destruction takes place faster than the hæmoglobin is eliminated by the kidneys

or converted into bile pigment by the liver, the color index is apt to be above normal during the attack, though it falls below normal later when blood regeneration has begun.

Post mortem, the kidneys of a rapidly fatal case are found to be enlarged and congested, "the tubules blocked with hæmoglobin infarcts, the cells laden with yellow pigment grains."

Symptoms.—The *prodromes* are identical with those of a malarial attack, viz., malaise, lumbar pain, sense of heaviness and apathy, with mild headache and anorexia.

The actual commencement of the disease is usually with severe and prolonged rigor and rapid rise of temperature to 104° or 105°. In some cases the initial rise is slight, not exceeding 100°. The attack may even run a nonfebrile course. There is restlessness, with sense of oppression and hopelessness. After a few hours there is usually a transient perspiration with only slight remission in the fever, followed by a second and perhaps even by a third rigor and exacerbation within the first twenty-four hours.

Generally from the beginning there is violent bilious vomiting with abdominal pain and intense thirst. There may be diarrhœa, the stools being bilious and at times tarry from the extravasation of blood serum containing free hæmoglobin into the intestine. Sometimes there is constipation instead of diarrhœa. The liver is apt to be enlarged and tender to pressure especially over the gall bladder. Enlargement of the spleen is the rule, though it may be masked by intestinal distention, tympanites being a frequent condition in blackwater fever. *Jaundice* appears early, generally within the first twenty-four hours, and increases rapidly. It is seldom very deep in color and it usually disappears within a few days.

The urine is almost invariably markedly reduced in quantity. Very early in the attack, sometimes even before the outbreak of the fever, the *hæmoglobinuria* appears, the urine being thick, opaque, and of a yellow, red, or blackish-brown hue. It usually, though not always, acid. The specific gravity is generally high, 1.030 to 1.032. The albumin, estimated by Esbach's method, is generally from .05 to .2 per cent. Biliary pigment and bile acid are often present. If the urine be shaken it forms a red or yellow froth. When allowed to stand, a copious sediment forms, which contains epithelium, grains and flakes of hæmoglobin, hæmatoidin crystals, and hæmoglobinuric casts. It is exceptional to find a few red blood corpuscles. The quantity of urine is diminished and its evacuation is frequent and painful. Occasionally there is complete anuria.

The attack inevitably produces a sudden and severe anæmia, and the bodily strength is lost with corresponding rapidity. There is a small and irregular pulse with dyspnoea, and hemorrhage from the nose is common; from the gums or in the skin hemorrhages are less common.

In fatal attacks, death is apt to occur during the second week of the disease. It may be the direct result of cardiac insufficiency, of thrombosis or embolism, or of the severe blood dyscrasia. From the inability of the kidneys to perform their function death sometimes ensues from *uræmia* with all the usual symptoms of that condition.

The albuminuria persists usually for weeks, but in favorable cases the hæmoglobinuria is transitory and the jaundice disappears rapidly. Recovery is slow, with a gradual regeneration of the normal blood elements. As the parasites have undergone destruction along with the corpuscles containing them, a convalescent case frequently remains free from malaria for a long time without the administration of quinine. Hæmoglobinuric attacks have been known in several instances to terminate permanently a chronic malarial infection.

Diagnosis.—The presence of malarial parasites in the blood early in the disease, and their absence later, is an important fact. The presence of parasites in the peripheral blood after the second day of the disease, if

the case be not seen earlier in the attack, is against a diagnosis of blackwater fever and in favor of ordinary bilious remittent malaria. The most important differential diagnosis to be made is that from *yellow fever*. The discovery of parasites by an early blood examination, and the enlarged and tender liver and spleen are against yellow fever. The sthenic features present at the outset of yellow fever, the throbbing headache, flushed face, injected conjunctivæ, congested gums tending to bleed at a touch, are absent in blackwater fever. The points for differential diagnosis may be tabulated thus:

BLACKWATER FEVER.**YELLOW FEVER.**

Asthenic.	Sthenic.
Spleen almost always enlarged and palpable.	Spleen not enlarged.
Liver enlarged and painful.	Liver enlarged, not painful.
Early vomiting bilious, not bloody.	Early vomiting acid and mucous.
No late vomiting.	Late vomiting bloody (<i>black vomit</i>).
Jaundice early, and always present.	Jaundice late, perhaps absent.
Hæmoglobinuria, not hæmaturia.	Sometimes hæmaturia, but not hæmoglobinuria.
Sporadic.	Epidemic.
Wide distribution.	Limited distribution.
Attacks old residents mostly.	Attacks new residents mostly.
Predisposes to further attacks.	Produces immunity.

Prognosis.—This is always grave. A mortality as low as 4 per cent. has been observed by O'Neill in Madagascar, but the usual mortality to be expected is much higher, usually from 25 to 40 or 50 per cent. If a single attack followed by recovery is to be considered as a case treated and a large percentage of recoveries are returned on this basis, it should be remembered that if the patients were followed through subsequent attacks the individual mortality would be found to be much higher. According to Fisch, blackwater fever has become more frequent on the Gold Coast of late years, but the mortality has fallen from 50 to about 20 per cent. Favorable signs are the occurrence of only one or two brief febrile paroxysms lasting a few hours, and the rapid disappearance of the jaundice and hæmoglobinuria.

Prophylaxis.—The prophylaxis of blackwater fever is the prophylaxis of malaria and has to do entirely with protection of persons from the bites of mosquitos. Individual prophylaxis is a question of screening, and public prophylaxis a question of mosquito extermination. We are not as yet in possession of any evidence that blackwater fever is due to any special form of parasite. The use of quinine as a prophylactic will be discussed under treatment.

Treatment.—A patient attacked with blackwater fever should be put to bed at once. The surface of the body should be kept warm, draughts and chilling avoided, copious warm drink given if retained, and, if not, copious hypodermoclysis practised with physiological salt solution. Heat should be applied to the loins. As in other forms of malaria, a mercurial cathartic, calomel or blue mass, may be advantageously administered at the outset. Chloroform, tannic acid, sodium salicylate, and other drugs have been credited by various reporters with good effects in this disease. In high degrees of anæmia, oxygen inhalations would be indicated if practicable. Transfusion of blood has been successfully practised. If there be suppression of urine all irritant diuretics should be carefully avoided. The drug of prime importance in this as in other forms of malaria is, of course, *quinine*. When and how shall it be administered?

The writer's view of the so-called *prophylactic* use of quinine is as follows: A very small daily dosage of qui-

nine is often sufficient to inhibit the symptoms of the malarial paroxysm. In the malignant forms of malaria which prevail in the tropics this small dosage is not sufficient to cure existing infection. Such use of quinine does not, of course, bring about any sort of physiological immunity to disease. As a matter of military or other expediency, the efficiency of a force may often be preserved or enhanced by that small dosage of quinine which will inhibit symptoms without producing inconvenient cinchonism. But there is no acceptable evidence on record that this so-called prophylactic dosage will destroy the sporozoites implanted by the mosquito or prevent their further development. If malarial infection has taken place the patient needs more than this dosage for his cure. If no infection exists he needs no quinine at all.

As regards the use of quinine in the treatment of black-water fever, it should not be forgotten that the disease itself destroys primarily those red corpuscles whose resistance is lowered by the presence of parasites, and destroys the contained parasites along with them. There is thus a tendency to spontaneous cure. Kohlstock, F. Plehn, A. Plehn, and many of the French colonial physicians have treated series of cases of black-water fever without quinine, and with lower mortality and better results than are secured in other series treated with quinine.

Bastianelli's rules governing the administration of quinine in blackwater fever would seem to be sound. They are—

(a) If hæmoglobinuria occurs during a malarial paroxysm, and parasites are found in the blood, quinine should be given.

(b) If parasites are not found, quinine should not be given.

(c) If quinine has already been given before hæmoglobinuria appeared, and no parasites are found, stop it; if parasites are found, continue it.

When the administration of quinine is indicated in blackwater fever, it should be given intramuscularly, with scrupulous attention to asepsis. Brem recommends the bihydrochloride of quinine, the solution being made in the strength of 1 to 3 and with an excess of acid.

J. F. Lays

¹ Practical Study of Malaria. London, 1904.

² Malarial Diseases. Philadelphia, 1905.

³ Diseases of Warm Countries. Philadelphia, 1905.

⁴ Journal of the American Medical Association, 1906, xlvii, 1896.

BLOOD-VESSELS, PLASTIC SURGERY OF THE.

—The plastic work upon the blood-vessels has been carried out on entirely different lines from those followed in the development of plastic work upon the heart. It is significant that although the heart is the integral element in the vascular system, the operative work, now very extensive in amount, which has been carried out upon this organ, bears practically no relation whatsoever to that of a more limited character, and somewhat more recent date, done upon the blood-vessels. Indeed, the problems presented by these two distinct portions of the vascular system are so utterly different that there is perhaps no reason why any correlation between them should be looked for. In the case of the heart, the wall is dense and thick; hemorrhage from it cannot be controlled, except by direct measures, and its position in the thoracic cavity calls for the employment, at least in experimental work, of artificial respiration. The vessels, on the other hand, are tenuous and thin-walled; provisional hæmostasis is easily maintained, and, as a rule, the vessels operated upon lie in superficial regions. It is interesting, therefore, to note that for morphological reasons the plastic surgery of the central and peripheral portions of the vascular system, physiologically one, are in point of technique widely separated.

A further difference is to be noted in the fact that much of the progress in cardiac surgery has been gained in the primary work done upon human beings, whereas

the surgery of the vessels has been brought to its present state of relative perfection mainly through animal experimentation. Because of the very unsettled condition of vascular surgery, it is obviously impossible to present any satisfactory classification of the subject. Matas has made a provisional classification of operative procedures as follows:

ANGIORRHAPHY.—A. *Suture of Arteries*.—Arteriorrhaphy: (1) Lateral (a) with aids, obsolete; (b) without aids; avoiding intima or perforating all coats (through-and-through suture). (2) End-to-end (a) By suture, direct marginal suture without invagination (Carrel); confrontation of everted intima with U-sutures (Jaboulay) for through-and-through interrupted suture (Salomoni *et al.*); invagination (Murphy *et al.*). (b) With extravasal "aids," ivory clamps, decalcified-bone rings, ivory cylinders, grafted section of vein or artery, rubber sheaths, horn clamps, aluminum rings, magnesium rings (Payr). (c) With endovasal "aids," caramel cylinders (Carrel); Glass cylinders (Abbe).

B. *Suture of Veins*.—Phleborrhaphy: (1) Lateral. (2) Circular, (a) with suture, (b) with "aids."

A glance at this classification, which is the most comprehensive as yet advanced, shows at once the difficulties of classifying a subject which is still virtually in an experimental stage. While this is true of vascular anastomotic work, it can hardly be said of the suture of wounds in arteries and veins. These wounds, furthermore, are of frequent occurrence upon the operating-table, both those resulting from initial traumatism and those accidentally produced by the surgeon's knife. An attempt to suture such a wound occurring in a vessel and uncomplicated by a destruction of its continuity was the first natural step toward a suture of the entirely divided organ.

A general recognition of the healing power of arteries and veins when properly united came very slowly. In 1904 von Bergmann made the following limited reference to arterial suture: "When complete occlusion of the injured vessel involves direct danger to life, . . . then suture of the arterial wall may be performed."

Arteriorrhaphy is indicated in wounds of an artery, either longitudinal or transverse, occupying more than half the circumference, and in cases of complete section.

Although the lateral suture was first practised upon an artery in man in 1759 by Hallowell, an English surgeon, it remained for the aseptic era to develop the possibilities which were opened up by this fortuitous event. Schede successfully introduced a venous suture in 1882. Jassinowsky in 1889 proved conclusively that arterial wounds might be sutured with the preservation of the lumen of the vessel. His conclusions were as follows: (1) Arterial suture heals by first intention. (2) Bleeding can be avoided. (3) Hemorrhage and thrombosis need not be feared. (4) All clean longitudinal and oblique and flap wounds of large vessels, and transverse wounds not exceeding one-half the vessel circumference, should be sutured. Strict asepsis is necessary.

Murphy in 1897 came to the conclusion that: (1) A good technique is necessary for success in vessel suture in addition to the most thorough asepsis. (2) The very greatest gentleness should be practised. (3) The hæmostasis must be complete. (4) Silk should be used and should not penetrate the intima.

In 1899 Dorfner published the result of twenty experiments, sixteen being cases of arterial wounds with twelve successful results, and four being sutures of completely divided arteries. One of his most interesting comments was that slight pressure would control the moderate oozing which always takes place from the stitch-holes. This is significant, inasmuch as it suggests a certain amount of thrombus formation, even in successful cases.

Repair.—The healing process of arterial wounds is as follows: The incision fills with blood and fibrin, there being only slight deposits within the lumen, about the suture and the inner aspect of the wound. These de-

posits are very early covered with endothelium. Soon blood-vessels make their way into the adventitia and the media. They enter the clot and organize it. There is then a retrogressive process and a development of fibrous substance, which is later modified with elastic elements which eventually become quite marked in the region of the scar.

The technique of closing arterial wounds is thus described by Bickham. It refers to the invagination method, a technique now discarded in favor of circular suture: "With aseptic precautions [Carrel and others hold that asepsis is the very essence of success in all blood-vessel work] a sheath of the artery is exposed and opened with minimum injury. The circulation is controlled with broad-bladed rubber-padded forceps or by means of floss silk. A fully curved round conjunctival needle penetrates the adventitia and muscularis down to but not through the intima. The knots are interrupted and from 1 to 2 mm. apart. The sheath is separately sutured. Longitudinal wounds tend to gape more than transverse wounds. If the vessel be one-half cut through, it should be severed and reunited, preferably by invagination."

From a demonstration of the relative ease and safety with which rents or cuts in the vessel wall might be repaired, it was a natural step, but one somewhat tardily taken, to the removal of foreign bodies, thrombi and emboli, from the vessel lumen. In 1896 Sabanajew opened the femoral artery, hoping to find the cause of a rapidly developing gangrene of the leg. Lejar in 1902 reported a similar operation done upon a man aged 26 years who had sustained a severe contusion in the left inguinal region. Gangrene developed, and although the clot was removed, amputation later became necessary. The most recent report on arteriotomy for thrombosis and embolism is that of Stewart (*Annals of Surgery*, September, 1907). He successfully located a large clot in the femoral artery and closed the vessel with through-and-through silk sutures. The circulation was immediately reestablished, but it ceased in a few moments. The stitches were removed and the clot again washed out, this being followed by autolavage induced by momentary release of hæmostasis. The clot reformed, however, and was again removed, only to return. A portion of the vessel was then resected somewhat after the manner and for the same reason as resection may sometimes be indicated in the region of intestinal obstruction. Removal of the injured endothelial lining, however, failed to serve the purpose, and amputation was finally resorted to. The postoperative outlook after the attempted removal of an embolus would therefore seem to be more favorable because of the more normal condition of the vessel walls. It seems theoretically probable that the immediate traumatism to the endothelium, which accompanies a careful arteriotomy and closure, particularly if an abundant supply of vaseline be used, even in addition to the traumatism made by the lodgment of the embolus, will together have less weight in thrombus formation than the unknown pathological conditions which appear to exist at the site of a thrombus which forms from no apparent cause.

A glance at the recent literature on blood-vessel suturing demonstrates that, owing very largely to the activities of Carrel, the technique of end-to-end anastomosis and of the many subsidiary vascular operations has been so simplified as to be now a matter largely of personal handicraft and attention to detail. Not to any such fortunate degree, however, has the simplification of the matter come in regard to thrombus formation. For, although in the deft hands of Carrel and some other workers, thrombus formation occurs less rarely than in the practice of the less skilled, it is still the part of the problem least near to solution.

At the beginning of 1908 it may be stated that the status of blood-vessel surgery is as follows: After going through an evolution which bears many remarkable relationships to that which is so well known to have marked

the development of intestinal surgery—the use of all forms of mechanical aids whether intravascular or extravascular—surgical opinion is now almost unanimously at rest in its decision that such aids are to be dispensed with and that the use of the simple end-to-end through-and-through sutures by continuous stitch is the technique of choice. It has taken more than ten years to reach this conclusion, and it is unfortunate that the technique now so beautifully clear and so easy of accomplishment, owing very largely to the patient work of Carrel, should as yet be limited by the occurrence of a pathological phenomenon for the entire control of which no method has as yet been advanced. This condition is thrombosis. Because of the very intimate relationship of this complication to the subject under discussion, some further reference to recent theories as to its etiology is indicated.

Prudden classifies the determining causes of thrombosis as: (1) Those associated with the slowing of the blood current; (2) those relating to changes in the wall of the blood channels; and (3) those involving such alterations in the blood itself as to favor coagulation. The first are usually the result of weak heart action and they not infrequently occur in the veins. Such stagnation thrombi are also formed when, under favorable conditions, an aneurism is healed by digital compression, or again where the current is artificially slowed by the direct application of a constricting agent to the wall of the vessel. Such constriction has been applied in the course of experimental work by Halstead and his pupils. Similar thrombi are also formed in the ordinary course of ligation of vessels. That pathogenic bacteria are active agents in the formation of thrombi which result in changes in the walls of the vessel is adduced by the fact that they are common in acute infectious diseases, such as endocarditis and septicæmia.

With the systemic conditions in the blood itself which favor thrombosis, blood-vessel surgery has less to concern itself. Nevertheless, it is worth noting that in addition to the overcoming of the obstacles in connection with practical determination and prevention of thrombosis arising from one or other or both of the already cited causes, there might under unfavorable conditions be added an element of still bigger character, one which at present is practically unknown. Carrel believes that the very lowest grade and slightest degree of infection, one which under ordinary conditions will not produce pus, but which may perhaps be the cause of the postoperative rise, almost always seen after any operation, may be the cause of the thrombosis which, with harassing frequency, follows even upon the most masterly vascular operations. From our present interpretation of the action of pyogenic bacteria, it is somewhat difficult to understand just how it is possible for them to produce immediate thrombosis. For we have become accustomed not to look for any systemic or tissue changes resulting from bacterial infection short of at least twenty-four hours after their implantation. Nevertheless it is by no means to be denied that, despite the fact that thrombus formation may be seen occurring within the vessel almost directly after its suture, the presence of pyogenic organisms may cause an immediate response, the very first sign of which is a local increase in the coagulability of the blood. Jawkowski and Welch have indeed shown that bacterial toxins favor thrombus formation. Groves (*The Hospital*, December 8th, 1906) calls attention to the fact that certain nucleoproteins favor intravenous coagulation, as does an excess of carbon dioxide in the blood. This latter has probably a part in nature's protective system for preventing hemorrhage by shallowing the respiration as in fainting. Significant and perhaps holding a definite relation to Carrel's former assumption that thrombosis after suture is due to a very mild infection is the well-known fact that a large percentage of postoperative thrombosis is known to have followed operations which in themselves and in their clinical manifestations were, in the ordinarily accepted use of the term, aseptic. At

present Carrel considers physiological conditions to play at least an equal part with infection.

The Carrel Technique.—In 1902 Carrel published his technique of circular suture. It did not differ materially from the methods before described, except in its strict attention to facilitating details. These, while small in themselves, came at just the right time and contributed more than any other factor to put arterial and venous suture on their present firm footing. In brief, Carrel's method is as follows:

First, absolute sterility. Second, the employment of exceedingly fine, round needles, and a Chinese silk suture which completely fills the eye. These sutures are white and are caused to stand out in relief by the employment of a black silk background; the latter aids the operator's eye in detecting the whereabouts of the needle, and is a very essential element of success; it surrounds the entire wound and is carefully tucked under the field of operation. Third, the free use of sterile vaseline. Suture material is best prepared by sterilizing directly in this material. The blood-vessel is thoroughly coated with it both within and without. Fourth, the provisional hæmostasis is not maintained by the direct action of clamps, but by the pressure of elastic bands which are made tense by clamps applied at the vessel's side. An exception is made in the case of large vessels, the Crile clamp being then indicated. Fifth, every particle of clot is most scrupulously washed away prior to ligation. Sixth, through-and-through sutures are placed between both walls 120 degrees apart. Seventh, the needles are left on these, an assistant holding one, the operator holding the single thread of the other in the left hand, sewing toward the assistant. As each 120 degrees is completed, the suture is tied to the succeeding traction line and the suture line is continued.

Whereas in 1902 Carrel advised the avoidance of the intima, he now appears to have shown that it can be penetrated with impunity, thrombosis having no direct relation to its puncture, for although there is the wound the trauma is reduced to a minimum.

In addition to the studies upon the effect of arteriovenous anastomosis in various forms of aneurism, some very interesting observations have been deduced from the conditions said to arise after the implantation of a large artery into a small vein. Carrel and Guthrie believe that they have succeeded in producing an actual arterial sclerosis by this procedure, the microscopical and histological changes conforming very closely to those found in the usual pathological subjects. This question is, however, intricate and as yet unsolved. The arterial wall reacts first by a hypertrophy of the muscle layer, the sclerosis of the intima and adventitia following. Conversely when arterial tension is lowered by the anastomosis of a small artery into a large vein, the wall of the artery becomes attenuated and its lumen grows larger.

Termi-no-terminal Anastomosis.—This is the designation of the operation by which the central end of an artery is connected to the peripheral end of the corresponding vein, or the peripheral end of the artery to the central end of the vein. Carrel and Guthrie, who made these observations, noted that: (1) At first the valves prevent reversal of the circulation; (2) in a short time (usually twenty minutes) they gradually yield, and arterial blood flows through the veins as far as the capillaries; (3) after some delay it passes the capillaries, and the arteries fill with venous blood; (4) three hours after operation there is a complete reversal of the circulation.

Their further experimentation in this line is of particular interest as bearing on the treatment of senile gangrene. They found that a lateral arteriovenous anastomosis permitted the return of most of the arterial blood through the central end of the vein. Sufficient impact was given the venous circulation to cause the peripheral venous radicals to distend and pulsate, but

not sufficient to force the arterial blood through them. This probably accounts for the failure of the cases of lateral arteriovenous anastomosis for the treatment of aneurism, and demonstrates that very little can be done on the human being until the matter is thoroughly demonstrated by animal experimentation. Probably in case of lateral anastomosis the vein should be tied just central to the point of anastomosis.

Vasal Transplantation.—Watts (*Annals of Surgery*, September, 1907) states that transplantations of arteries and veins may be complete or incomplete. In complete transplantation, the segment of vessel is completely excised and then sutured between the cut ends of the other vessel. Carrel denominates as "autoplastic" a transplantation in which the section of vessel is taken from one vessel and transplanted into another of the same animal, a "homoplastic" transplantation being one in which the section of vessel is taken from another animal of the same species. A "heteroplastic" transplantation is one in which the section is taken from an animal of a different species. These sections have recently been kept in cold storage for long periods of time and have retained their ability to act as living grafts. This remarkable demonstration reminds one of the well-known ability of certain forms of skin grafts to functionate after having been kept for months.

Replantation and Transplantation of Organs and Limbs.—Watts says that "the replantation of an organ or limb consists in removing it, replacing it, and re-establishing its circulation by vascular anastomosis. The transplantation of an organ or limb consists in its removal and transplantation into another animal, or a different portion of the same animal, its circulation being re-established by vascular anastomosis."

To Ullmann (in 1902) is probably due the credit of the first transplantation of a dog's kidney into his neck. This was done by means of Payr's protheses. According to Carrel and Guthrie there are two methods of transplanting organs, viz., simple and *en masse*. The objection to the simple transplantation is that the nerves and their sympathetic ganglia are cut off. To obviate this, the idea was conceived of removing the organs, particularly the ovaries and testicles, with a large mass of tissue adherent to them. Carrel states that whereas he was formerly solicitous about the arterial supply, he has come after long experience to recognize that success in transplantation is due far more to the presence of venous drainage than to the perfection of arterial supply. He therefore in his present technique takes much greater pains with the veins than with the arteries.

Therapeutic Application.—A further attempt at surgical therapy has been made in efforts to transplant the thyroid gland. Watts reports six cases—all in dogs and all unfortunately unsuccessful.

From a study of the suggestions which have been thrown out as to the possibilities which vasal surgery offers in the line of surgical therapy, it will be seen that an effort is being made to locate and remove thrombi and emboli. In the exercise of this therapeutic measure, two marked difficulties present themselves. The first lies in determining the location of the lesion, and here should be noted that the pain is referred, not to the site of the lesion, but to the region of ischæmia produced by it; the second lies in preventing the reformation of a thrombus after the original clot has been washed away. On these two important points no doubt more light will soon be cast.

Of the treatment of various forms of gangrene but little can be said except that the failures reported in attempts upon human beings corroborate the experimental findings. That a lateral arteriovenous anastomosis is valueless, and a direct severing and reunion of the vessels necessary are rather clearly indicated. That even this would be productive of good there is, however, not yet definite proof.

Transplantation of vessel segments is as yet in an undetermined condition. When there has occurred

any extensive destruction of an arterial wall, and in the event of such artery being accompanied by satellite veins, one would naturally turn to one of the additional veins as a source of supply for the graft. Unfortunately, however, the weight of experimental evidence is against the employment of vein tissue to bridge arterial defects, because, although every effort has been made to strengthen the wall, even so far as doubling it back upon itself so as to give twice the usual thickness to the vein wall, the result has not been gratifying. This corroborates the belief that there is an intrinsic element in the arterial wall particularly adapted for pressure. That this is quite wanting in the vein wall is shown by the fact that even a double thickness soon pouts out, producing an aneurismal condition of the vessel.

Carrel has carried on some researches upon the effect of reversing the blood current in the thyroid of goitrous dogs. At the Johns Hopkins Hospital, Watts has essayed the transplantation of the thyroid gland six times, as already cited, without success. He attributes the failure to the small size of the inferior thyroid vein and perhaps also to his unfamiliarity with technical details.

This represents another separate and distinct effort on the part of experimental surgeons to introduce a surgical method in the treatment of pathological conditions of the thyroid, through the medium of arterial suture.

Perhaps the boldest and most significant attempt to cure a human ailment through the medium of vasa suture has been reported in the heroic efforts to transplant a healthy kidney in place of a diseased organ. Efforts in this direction have been made quite continuously by a number of experimenters since Ullmann's work in 1902, already referred to. Carrel has succeeded in maintaining a flow of urine from a transplanted kidney for upward of two weeks. The urine secreted by the transplanted organ was of almost normal character, and contained but little albumin. In view of a confessed failure of all methods so far suggested by the medical world to retard in any way the various processes of an advancing nephritis, no one can surmise without interest from the standpoint of human therapy what may be the brilliant future of such amazing experiments.

The deepest niche in the experimental stairs was cut in 1903, when Hopfner amputated and replanted dogs' legs. It was but a short step from this work to the transplantation of entire members from one dog to another. The overwhelming difficulties of this procedure have thus far baffled all attempts to obtain a functioning member either from replantation or from implantation. Nevertheless, a good circulation has been maintained for a number of days in the amputated member. And although, up to date, thrombosis followed by death of the part has invariably occurred, those would be rash who in the face of to-day's attainments would predict that success might not follow to-morrow.

In conclusion, then, the general status of blood-vessel surgery may be summed up to date as follows: The surgery of the blood-bearing tubes has passed through an evolution not unlike that which took place in relation to the tubes of the alimentary system. In each, there was first the effort to restore wounds where the continuity of the vessel was unbroken. In each there was a magnificent display of ingenuity on the part of the surgeons who sought to devise intravascular or extravascular aids. The number and character of these, both in intestinal and in arterial experimentation and practice, have been truly astonishing. The surgery of the intestinal canal has always been several years in advance of the surgery of the blood-vessels. The result of this is that all aids were discarded in intestinal work some years ago, in favor of the simple suture. Aids in vasa surgery are, however, only just being recognized to be equally useless, the suture taking their place. When one considers the morphological similarity of the intes-

tinal and circulatory tubes from a standpoint of surgical technique, it may be confidently predicted that the newly made decision in favor of the suture for arterial and venous work is logical and will in the future entirely supplant all mechanical devices, as has been the case in intestinal surgery.

J. W. Draper Maury.

BRONCHIECTASIS.—Dilatations of the bronchi, either diffuse or circumscribed, are known as bronchiectases. They are of common occurrence and arise from a great variety of causes. In all cases, however, the essential cause of bronchial dilatation is to be found in a weakness of the bronchial wall or an increase of pressure within the bronchus, or in a combination of both these factors. Bronchiectases appear both clinically and pathologically in such a variety of forms that their classification is difficult. According to their etiology they may be divided into the following forms:

- | | | |
|-----------------|---|-------------------|
| Bronchiectasis. | { | 1. Congenital. |
| | | 2. Atelectatic. |
| | | 3. Vicarious. |
| | | 4. Emphysematous. |
| | | 5. Inflammatory. |

GENERAL MORBID ANATOMY.—The condition of bronchial dilatation may be single or multiple, one or more of the bronchi being affected. In some cases the entire bronchial tree is dilated (*universal bronchiectasis*). When but one bronchus is dilated the condition is usually found in the upper lobes; when many are dilated the lower lobes are affected. Usually the bronchial branches of the third or fourth order are the ones involved; they not infrequently become wider than the main bronchi, and may

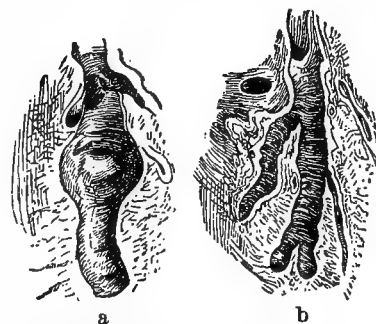


FIG. 5130.—Saccular and Cylindrical Forms of Bronchiectasis. (After Orth.) a, Saccular form; b, cylindrical form.

on section resembling a very porous cheese.

The dilatation may be more or less uniform (*cylindrical, fusiform, or spindle-shaped bronchiectasis*), or it may be localized, the dilatation being much greater at one point than elsewhere, or involving but a small portion of the bronchus (*saccular bronchiectasis*). In other cases a succession of dilated portions may be separated from each other by portions of the bronchus which are of normal width or are constricted (*varicose or rosary bronchiectasis*). The different forms may be found in the same lung. Closure of the central end of the dilated portion and the accumulation of secretions may give the dilatation the character of a cyst (*bronchiectatic cyst, cystic bronchiectasis*). Suppuration of the wall of the dilated bronchus gives rise to the conditions known as *ulcerative bronchiectasis* and *bronchiectatic abscess*. Enlargement of the bronchiectasis at the expense of the surrounding lung tissue leads to the formation of bronchiectatic cavities (*cavernous bronchiectasis*). Infection of the dilated bronchus with putrefactive organisms causes a *gangrenous bronchiectasis*. In this case also the destruction of the wall of the dilatation and the encroachment upon the surrounding tissue give rise to the formation of cavities. In some cases the larger bronchi may be chiefly affected, in which event the

often be followed out to the pleura, where they end generally in a sac-like terminal dilatation of somewhat greater width, as is seen in Fig. 5130, b). In other cases the terminations may be of normal width, or they may become narrowed. The smaller bronchi may at times alone be dilated, the lung

distended portions project from the main bronchus like the dilated fingers of a glove.

The walls of the dilated portion may appear to be normal, or they may show marked pathological changes.



FIG. 5131. — Atrophic Cylindrical Bronchiectasis with ribbed transverse markings. (After Ziegler.)

The inner lining may be smooth or roughened. The smooth-walled dilations often contain no fluid. As a rule the bronchial mucosa presents the appearances of a chronic purulent catarrh. The cylindrical epithelium is usually replaced by one of a cubical or squamous type. In the large saccular bronchiectases and in some of the cylindrical forms due to retained secretions the lining membrane may be ulcerated. Polypoid outgrowths are not infrequently seen. The contents of the cavity may be thin and watery, or thick or even caseous. In some of the larger bronchiectases, and particularly in the case of secondary gangrene, the contents are horribly fetid. Microscopically the fluid consists of mucus, pus corpuscles, fatty acid crystals,

and occasionally blood and hæmatoidin crystals. In the case of ulcerative or gangrenous conditions of the walls elastic fibres may also be present. The outer portions of

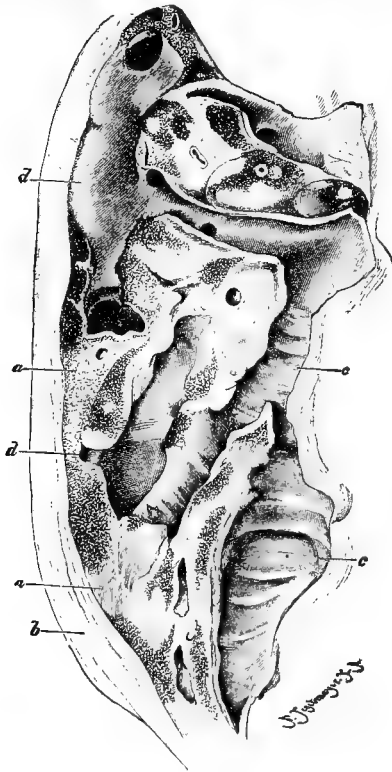


FIG. 5132. — Hypertrophic bronchiectasis and bronchiectatic caverns in fibroid induration of lung. (After Ziegler.) a, indurated lung-tissue; b, thickened pleura; c, dilated bronchus; d, cavity communicating with a dilated bronchus.

the wall of the dilated portion may be markedly atrophic; even the cartilage plates may entirely disappear. The elastic tissue is stretched and separated; and the muscle, if it has not entirely disappeared, is much stretched and atrophied. The mucous glands may also

entirely disappear, or may show extreme mucous degeneration. In other cases a secondary thickening of the wall, due to a new formation of connective tissue and elastic fibres, may occur. This is true particularly of the inflammatory cases. Small-celled infiltration of the wall is usually present. According to the condition of the bronchial wall bronchiectases may be divided into the *atrophic* and the *hypertrophic* forms. Such a classification has, however, but little practical importance, inasmuch as both forms may be found in the same lung. In general, the condition of the wall is dependent essentially upon the cause of the dilatation.

The *atrophic form* occurs in association with emphysema, and as a sequela of old chronic inflammatory processes which lessen the elasticity and resisting power of the bronchial wall, so that it gives way to the air pressure. Prolonged and difficult expiration favors its occurrence. Such dilations are usually cylindrical and occur chiefly in the bronchi of the lower lobes. Very often the stretching of the bronchial wall is not uniform, and the inner surface shows circular or oblique ribbed elevations corresponding to circular bands of muscle fibres and elastic tissue which are still preserved, the connective tissue between them being pushed outward. All the elements of the wall are more or less atrophic, even the cartilage, which may be replaced by connective tissue containing newly formed blood-vessels. The openings of the mucous glands are dilated and funnel-shaped. The epithelium may be well preserved, or it may be changed to a cubical or flattened variety, or may be desquamated.

The *hypertrophic form* occurs as a frequent sequela of indurations and contractions of the lung parenchyma. In these cases the greater part of the lung is usually impermeable to air, and the cause of the dilatation is less a result of the weakening of the bronchial wall, but is essentially dependent upon an increase of intrabronchial pressure, which is due to the fact that the air entering the bronchi no longer passes normally into the ramifications of the air passages. In the case of retraction of the lung tissue with pleural adhesions the outward pull upon the bronchial walls is also an important factor in causing a dilatation of the bronchial lumen. In both cases the dilatation is favored by any inflammatory process which weakens the wall. The mucous membrane of the dilated bronchus in the hypertrophic mass may resemble that found in the atrophic forms, or papillary or polypoid proliferations may be present. A lattice-like marking of the lining membrane is often seen. These markings correspond to small thickenings or elevations of the mucosa corresponding to the formation of a very cellular granulation tissue about the longitudinal and transverse bundles of elastic tissue. The connective tissue of the wall and of the peribronchial region is more or less thickened and connective tissue may take the place of the mucous glands and cartilages. The capillaries of the wall are greatly dilated and present thickened walls. The hyperæmia of the wall may be so marked that the appearance of the mucosa suggests a hemorrhagic condition. Tuberculous and gangrenous processes may cause various modifications of these appearances.

The *saccular bronchiectases* usually develop at the cost of the lung parenchyma. The bronchus may show at some point in its course a dilatation varying in size from that of a mustard seed to that of a hen's egg, or the bronchus may terminate in a sac. The central end of the dilatation may become obliterated and the dilatation thus come to resemble a cyst. Through the accumulation of secretions the cyst may attain great dimensions. All the bronchi of one lung may be similarly affected, the lung tissue between becoming atrophic and compressed, so that the organ finally comes to resemble a multilocular cyst. In other cases the saccular dilatation may involve only a portion of the circumference of the wall, so that it appears as a diverticulum which is connected with the lumen of the bronchus by a narrow opening only (*dilatation ampullaire latérale* of Cruveilhier). In the majority of cases the saccular dilatations involve the smaller

bronchi, more rarely are the main branches affected. They are usually associated with bronchial stenoses, and are most often found near the periphery of the lung. According to Gairdner all the saccular dilatations are the result of ulcerative excavations of the lung tissue. This is true, however, of only a part of the cases.

Biermer divides bronchiectases, according to the character of their walls, into the following forms: (1) Dilatations with catarrhal swelling and relaxation of the bronchial wall. These are acute and occur chiefly in the lungs of children affected with chronic bronchitis. After the bronchitis has been cured the bronchial wall regains its old tone and elasticity, and the dilatation disappears. (2) Dilatations with hypertrophic walls. These affect the larger bronchi and are usually spindle-shaped. (3) Dilatations with thin walls. These are usually saccular. (4) Dilatations with trabecular degeneration. The walls are uneven, thickened, and there is a peribronchial increase of connective tissue.

Ulcerative processes are of common occurrence in the mucosa of the saccular bronchiectases. Complete destruction of the elements of the wall may take place, giving rise to a bronchial abscess. Infection with putrefactive bacteria leads to a secondary gangrene. Such changes are due to the lessened resistance of the bronchial walls, the changes in the secretions, and the entrance of bacteria. In these cases elastic tissue may be found in the sputum. Deposits of lime salts may occur in the bronchial walls, and as the result of the formation of granulating surfaces adhesions of the walls or the development of connective-tissue bridges may take place. In some cases a complete obliteration of the lumen results, and the bronchus is converted at the point of dilatation into a fibrous cord.

The changes in the lung tissue in the neighborhood of the bronchiectasis are usually primary, with the exception of ulcerative and gangrenous processes, which are secondary to the dilatation. The bronchi which are not dilated show catarrh and a putrid decomposition of the secretions. They are often wholly obliterated. In bronchiectases due to syphilitic affections of the air passages the dilatation of the smaller bronchi is usually secondary to a stenosis of the trachea or large bronchus. The portions of the lungs not affected by the condition causing the bronchiectasis may present a compensatory emphysema, and in the later stages foci of bronchopneumonia, due to the aspiration of secretions from the dilated bronchi, may be found. The right ventricle may become hypertrophied and dilated as the result of the stasis in the pulmonary circulation. The bronchial glands are usually swollen.

Metastasis may take place from bronchiectases. Biermer observed metastatic brain abscesses in four cases of bronchiectasis; and Gerhardt and Bardenheuer noted the occurrence of rheumatic joint affections in patients with bronchiectases. Chiari has reported a case of suppurative myelitis following bronchiectasis. In the pus and vessels of the cord a branching filamentous fungus was found which showed threads breaking up into coccoid bodies and staining with Gram's mixture. Of eight cases of hæmatogenous myelitis collected from the literature three were secondary to bronchiectasis. In one case of actinomycotic abscesses occurring in the brain of a man with numerous bronchiectatic cavities, many clusters of the fungus were found in the walls and contents of the latter.

LOCATION.—Statistics as to the location of bronchiectases are of doubtful value. This is particularly true with regard to the relative frequency of involvement of the right and left sides and the upper and lower lobes. The statements generally made in regard to these points are to the effect that bronchiectases usually occur in one lung, and more frequently on the left than on the right side, and more often in the upper lobe than in the lower, and that in double-sided bronchiectasis both upper lobes are more often affected than the lower ones. But little importance can at present be attached to such statements, the number of observations upon which they are based

being too small. The dilatations occurring with tuberculosis and chronic inflammatory processes are more often seen in the upper lobes; in the case of pleuritic exudations, in the compressed lower lobes; in those occurring as sequelæ of croupous and catarrhal pneumonia, hypostatic and atelectatic conditions are found in the lower and posterior portions. In the case of pleural adhesions the dilatations are sometimes found in the bronchi of the upper lobe, sometimes in those of the lower lobe.

Congenital Bronchiectasis.—Under this head there is included a number of conditions in the lungs of the newborn which have been regarded as due to congenital syphilis. One lung is usually affected; it may contain numerous cysts filled with a serous fluid. The lung tissue between the cysts may be indurated or atelectatic. Heller, Herzheimer, Grawitz, and others have described cases which, according to Grawitz, are to be ascribed to a hydropic dilatation of the bronchi. Heller regards them as representing the bronchi of undeveloped portions of the lung, the dilatation occurring in later life partly as the result of the growth of the thorax and the consequent pull upon the bronchus, and partly as the result of the growth of the bronchus itself and the pressure of retained secretions.

Atelectatic Bronchiectasis.—The congenital bronchiectasis of Heller is to be placed in this class. In a number of cases observed bronchial dilatations have been found in adults, the lung tissue being free from pigment and showing no evidences of inflammatory changes. The condition is therefore very probably the result of a congenital atelectasis. An acquired bronchiectasis, due to atelectasis, may take place in later life as the result of deformities of the thorax, tumors, aneurism, etc.

Vicarious Bronchiectasis.—If the entrance of air into any portion of the lung be hindered and the volume of that part reduced, the inspiratory pull upon the sound portions of the lung is increased. As the result of this increased pull both the alveoli and the bronchi become dilated, and there arise a vicarious emphysema and a vicarious bronchiectasis. Pneumonic foci, infarcts, local atelectasis, local tuberculous nodules and infiltrations, contracting scar tissue, etc., are the causal factors of such bronchial dilatations. The bronchial wall and mucosa become stretched and thinned like a serous membrane. The essential characteristic of the change is that no inflammatory processes take part in the direct production of the dilatation. It is to be regarded as a vicarious emphysema of the bronchi. The clinical significance of the condition is not great. The dilatations are relatively small and circumscribed. Inflammatory changes may follow, and an ulcerative or inflammatory bronchiectasis develop.

Emphysematous Bronchiectasis.—An emphysema of the bronchi occurs also in simple atrophic emphysema of the lungs not due to a compensation for portions of the lung the function of which is lost or diminished. It is to be regarded as idiopathic rather than vicarious or compensating. The dilatation is not great, but the walls of the bronchi are greatly thinned. The smaller branches, particularly those of the lower lobes, are chiefly affected. The symptoms cannot be separated from those of alveolar emphysema.

Inflammatory Bronchiectasis.—This is by far the most common and important form. All authorities are agreed that for the production of a bronchiectasis of clinical importance an inflammatory weakening of the bronchial wall is necessary. In general there are no severe inflammatory conditions of the lungs or pleura in which bronchiectases may not develop. Capillary bronchitis, chronic bronchitis, catarrhal pneumonia, croupous pneumonia, particularly when running a subacute or chronic course, tuberculosis, obliteration of the bronchioles due to indurations, peribronchitis, typhoid hypostasis, stenosis of the large bronchi, pleuritis, pleural adhesions, etc., are the causal and predisposing factors. General anæmia, marasmus, alcoholism, excessive or forced respiratory movements, singing, screaming coughing, etc., play a secondary part. In the case of bronchial

stenoses the bronchus is usually dilated both above and below the point of stenosis. It is probable that the dilatation which lies below the stenosis is due to the fact that the air which passes through the stenosis into the portion of the bronchus below it is held there by the blocking of the stenosis with mucus during expiration, and as the result of the expiratory increase of pressure this portion of the bronchus becomes stretched. In the case of foreign bodies the bronchial dilatation is found not only around the body, but involving other bronchial branches as well. The causes of such dilatations are complicated, but the essential factor is the production of a peribronchitis. Tuberculosis and syphilis may give rise to bronchiectases which are primarily dependent upon stenoses caused by the contraction of scar tissue, or are due to infiltrations. Chronic pneumonia, whether following the acute pneumonias, or due to syphilis, pleuritis, foreign bodies, etc., or primary of unknown origin, is of especial importance in the etiology of bronchiectasis.

SYMPTOMS.—Cough.—This is the rule. It occurs in paroxysms, usually at long intervals, almost always on the patient's awakening in the morning, the paroxysm being repeated once or several times during the day. The patient may be awakened by the first paroxysm, or it may come on after arising. Usually the patients know the time when the attacks may be expected. A paroxysm may also be precipitated by the patient's lying upon the affected side and then turning suddenly into another position. The attacks are often very violent and convulsive, at times completely depriving the patient of breath. The frequency and severity of the cough are dependent upon the position and the character of the opening of the dilatation. As long as the secretions are retained within the cavity there is no coughing, but when these escape into the neighboring bronchi and alveoli paroxysms are excited. When the bronchiectasis is located in the apex the secretions may pass continuously into a vertical bronchus and thus give rise to almost constant coughing.

Dyspnea.—This may be slight or entirely absent; it usually increases in degree toward the later stages of the affection and may become very marked. Ordinarily it is noticed only at the time of coughing, or after vigorous exercise. It is increased in the event of acute catarrhs of the respiratory tract, and in the case of the collection of mucus in the smaller bronchi. Persistent dyspnea is due to some complication on the part of the heart or lungs.

Expectoration.—The attacks of coughing are attended by expectoration. This may resemble that of any ordinary bronchitis, but in the majority of cases the expectoration is very characteristic and of diagnostic importance. With the coughing paroxysm there is a gush of sputum so great as to fill the patient's mouth. Within a few minutes an ordinary sputum cup may be entirely filled. The total amount of sputum may be so great as to suggest the possibility of the perforation of an empyema into the bronchus or lung. Five to seven hundred cubic centimetres may be expectorated within the twenty-four hours. With the evacuation of the dilatation the coughing usually ceases, to begin again as soon as the bronchiectasis fills up. Usually the sputum is raised easily, without much effort or coughing, but in the case of such complications as pleuritis, emphysema, tracheal or bronchial stenosis, etc., the expectoration may be very difficult. The position of the patient is of great importance; when he lies upon one side there may be neither cough nor expectoration, but as soon as he turns upon the other side the bronchiectasis begins to empty itself and the cough and expectoration are excited. Sensations of pressure, fulness, and pain are sometimes felt before the expectoration takes place, particularly in the case of children. Occasionally these symptoms may be very marked, lasting half an hour or so before the expectoration occurs. The large amounts of sputum and the long periods between the attacks of expectoration may be explained as due to a lessened irritability on the part of the bronchial mucosa, a larger

quantity of sputum being necessary to excite coughing. The amount of sputum raised is always greater during the morning hours. Toward the end of the affection the total amount decreases as the patient becomes weaker.

Sputum.—The sputum is usually purulent in character, but may be fetid or gangrenous. When purulent it is yellowish and contains more or less mucus. If fetid in character the odor may be extremely disagreeable and penetrating, so that the patient's breath may be perceived some distance away. The patient himself shows a remarkable tolerance of the odor; nausea is rarely produced. In the gangrenous cases the sputum is grayish-yellow or greenish in color. When the complication of gangrene is not present the sputum may have no putrid odor, but commonly possesses a disagreeable, nauseating, acid or sweetish smell (pseudogangrene). When collected in a glass or cylinder the sputum separates into two distinct layers: an upper, thin, slightly cloudy, almost serous layer; and a lower, thick, purulent layer containing caseous masses. The latter appear as dirty yellow plugs varying in size from a mustard seed to a bean (plugs of Dittrich). If the sputum be put into a tall cylinder which is half filled with water, four distinct layers may be seen. The uppermost is foamy; the one beneath this consists of muco-purulent masses, which hang down in the form of shreds into the third layer, consisting of cloudy water. The lowest layer of water has a grayish-green appearance.

Microscopically the sputum is made up of pus corpuscles which may be well preserved or contain fat droplets. In the case of putrid decomposition bacteria, crystals of fatty acids, margarin, tyrosin, leucin, and triple phosphates may be present. Blood-pigment may also be found. In the case of gangrene elastic fibres may be present. The caseous plugs stain a brownish-yellow, blue, or violet with dilute iodine solutions. The mucin content of the sputum varies greatly. Blood cells are not infrequently present.

Hemorrhage.—The presence of blood in the sputum of bronchiectasis is not rare. The amount is usually small, but the hemorrhage may be so large or so frequently repeated that severe symptoms or even death may ensue. The sputum in such cases may appear to be chiefly blood; it is rarely bright-red, but is more or less discolored by the mixture with the other elements of the sputum. The smaller hemorrhages are chiefly of capillary origin; the large ones come from the erosion of large vessels in the wall of the dilatation. In ulcerative conditions of the wall the hemorrhages may be very severe, persist for a long time, and finally lead to death.

General Symptoms.—When secondary changes in the heart, kidneys, etc., are not present, the general condition of the patient may be quite good or fair. Fever and sweating are signs of complications. Occasionally fever may be caused by the absorption of products of decomposition from the cavity. In such cases the fever does not present any distinct type.

Physical Signs.—Inspection.—The color of the skin is usually unchanged. When it is very pale the underlying disease is most likely to be tuberculosis; when it is cyanotic there is usually emphysema present. Many of the patients lie upon their backs; others sit bending forward, claiming that this prevents the swallowing of the sputum. When the bronchiectasis is confined to one side, the patients usually lie upon the affected side, coughing and profuse expectoration being caused by turning upon the sound side. Deformities of the thorax are rare, occurring only in the case of retraction of the lung, or when extensive pleuritic adhesions are associated with the bronchiectasis. Diffuse or localized retraction of the thoracic wall and curvature of the spine may result from these conditions. When emphysema is present the thorax may present the characteristic barrel form. Occasionally differences of movement may be made out between the two sides. In the case of extensive bronchiectases of the lower lobe of one side there may be seen during deep inspiration a wave-like retraction of the intercostal spaces proceeding from above downward. On the affected side such

a movement is not visible. A compensatory emphysema of the sound lung is always found in such cases. Very rarely it may be seen that the respiratory movements on the affected side lessen, and at last wholly cease as the bronchiectasis fills up, but return after the expectoration has emptied the bronchus.

Among the most common and important of the physical signs of bronchiectasis are the changes which take place in the distal phalanges of the hands and feet (drumstick fingers). The clubbing of the fingers is due to a hypertrophy of the terminal portions of the bones (*ostéoarthropathie hypertrophiante pneumique*), so that the joints of the phalanges, the carpal joints, and even the wrist joint may be greatly thickened. These changes take place in association with chronic cyanosis and appear to be dependent upon the latter. They are also found in other conditions than bronchiectasis, particularly in the congenital heart lesions; but Bamberger has attempted to show that the change in bronchiectasis is characteristic of this affection, in that it is a painful hypertrophy of the epiphyses.

Percussion.—The percussion phenomena of bronchiectasis vary greatly, being dependent upon the size of the dilatation, the quantity of fluid present in it, its distance from the chest wall, and the character of the changes in the surrounding lung tissue. Dulness or a tympanitic tone may be obtained, or both alternately, according as the cavity contains fluid or air. A tympanitic tone with change of pitch on opening and closing the mouth may be noted, as well as change of tone on change of position, the cracked-pot sound, metallic tones, etc., according to the conditions present. About the areas showing such signs of cavity the tone may be resonant; in the case of tuberculous cavities it is always dull. The dislocation of the neighboring organs, pleuritic thickenings, adhesion, etc., may also be shown by percussion.

Auscultation.—The vesicular murmur is weakened or absent, being replaced by a bronchial blowing. The cylindrical dilatations give a soft bronchial sound, and when containing fluid they yield also moist, coarse bubbling râles. The saccular dilatations give both the percussion and auscultation signs of a cavity, particularly large, moist, bubbling râles.

COMPLICATIONS.—The most frequent and dangerous complication is the putrid or gangrenous decomposition of the contents of the dilatation. Pleuritis, peribronchitis, bronchopneumonia, chronic pneumonia, chronic bronchitis, lobar pneumonia, emphysema, chronic laryngitis, renal and cardiac affections, dropsy, albuminuria, cirrhosis of the liver, etc., may be associated with bronchiectasis or appear as sequelæ. Metastatic abscesses may occur in the brain, spinal cord, etc.; there may also be rheumatic joint affections. There arises in these cases a suspicion of the occurrence of a general pyæmic infection. Perforation of the dilatation into the pleural cavity leads to the development of a pyopneumothorax. In old chronic cases of long duration amyloid degeneration of liver, spleen, and kidneys may be found. Tuberculosis is a fairly common complication. The heart is usually affected, hypertrophy and dilatation of the right ventricle occurring in the majority of cases. The cardiac changes are due partly to disturbances in the pulmonary circulation, partly to the accompanying condition of chronic intoxication, partly to local changes in the thorax, and partly to coincident renal changes.

DURATION AND COURSE.—Bronchiectases may remain stationary for years, the only symptoms being those of a chronic bronchitis. As a rule the dilatation gradually increases during this time without an increase in the symptoms. With the advent of fresh catarrhs emphysema gradually develops, the shortness of breath becomes more marked, and the patient may become cyanotic. The right heart becomes hypertrophic and finally dilated. Putrid bronchitis and gangrene may occur; from these the patient may recover for a time, or death may take place. As a rule the condition runs for a long time; amyloid disease of the kidneys may finally result and the patient becomes dropsical. After alternating periods of

improvement and exacerbation, extending over a long period, the disease is brought to an end by some one of the complications.

DIAGNOSIS.—The differential diagnosis of bronchiectasis from its complications is sometimes very difficult. The absence of the tubercle bacillus will distinguish it from tuberculosis. When the latter process is combined with bronchiectasis the character of the sputum, the age of the patient, position of the cavity, habitus, etc., are points to be considered in the differential diagnosis. The history of the case is of greatest importance. It may be taken as a guiding principle that tuberculosis may lead to a bronchiectasis, but that a bronchiectasis rarely becomes tuberculous. Actinomycotic cavities may be distinguished by the presence of the fungus in the sputum. The rare localization in the lung of hydatids may also be easily diagnosed by the findings in the sputum. From pulmonary gangrene, abscess, putrid bronchitis, interstitial pneumonia, pyopneumothorax, etc., the differentiation is often impossible. The physical signs of cavity are of the greatest importance in so far as the differentiation between processes with cavity formation and those without is concerned. Much was expected from the use of x-rays in the diagnosis of bronchiectasis, but these expectations have not been realized. Only in the case of extensive peribronchial thickenings may aid be looked for by the use of x-rays.

TREATMENT.—In very rare cases self-healing of the bronchiectasis may take place. In children this may follow the cure of catarrhal bronchitis and the restoration of normal conditions of pressure. In extremely rare cases the bronchial cavity may be obliterated by adhesion of the walls of the cavity or through the formation of granulation tissue. Since in the great majority of cases such healing is impossible, the prophylactic treatment becomes of prime importance. The conditions (pleuritis, pneumonia, etc.) which lead to bronchiectasis should be appropriately treated with a view to the prevention of such dilatations. After the development of bronchiectases the chief therapeutic indication is to keep the contents of the dilatation—so far as lies in our power—aseptic. This can be perfectly accomplished only by residence in an atmosphere containing no bacteria. Removal of the patient to a suitable climate is the best means of avoiding the various complications of the affection. When this cannot be done the treatment becomes chiefly symptomatic and largely directed to antiseptic procedures. Inhalations of creosote, turpentine, menthol, eucalyptus, etc., and creosote vapor baths are recommended for this purpose. A number of writers speak favorably of the creosote vapor baths. These are, however, unpleasant and slow in operation, and do not always succeed in lessening the amount of the sputum. The crude creosote appears to be more effective than the various substitutes (vapo-cresoline, refined creosote, soluble cresol, etc.) which have been advised. Other writers have found success with guaiacol vapor baths after failing with creosote. The ordinary methods of giving such inhalations may, however, be a source of infection, as many of the forms of inhalation apparatus used are dirt traps.

Intralaryngeal injections of menthol, guaiacol, etc., have been advised by Rosenberg, Stewart, Campbell, and others, but are condemned by various writers because they give rise to constitutional disturbances, fever, and violent cough.

Subcutaneous injections of guaiacol (1 in 5) and creosote (1 in 5) in olive oil have also been recommended. They may give rise to inflammation and necrosis at the point of injection.

Intravenous injections of formalin (25–50 c.c. of a 1 in 2,000 solution of formalin in decinormal salt solution) have also been tried without success.

Injections of carbolic acid and menthol directly into the bronchiectatic cavity have also been suggested.

Murphy's method of filling the pleural cavity with air or nitrogen to such an extent as to cause a collapse of the bronchial cavity has been tried with some success. The

air should of course be thoroughly sterilized. About 170 c.c. of air or nitrogen are injected every second or third day.

Inhalations of oxygen may aid in reducing the odor of the sputum. Symptomatic treatment with expectorants (apomorphine, senega, ipecacuanha, etc.) may at times give relief or temporary improvement. Hemorrhage should receive appropriate treatment.

Inasmuch as the medical treatment is usually without avail, much had been hoped from surgical intervention in the treatment of bronchiectasis. This has now been given a very extensive trial, with complete failure in the majority of cases, and only partial success in the others. These unsatisfactory results are easily understood when we consider the facts that the dilatations are often multiple and bilateral, and that the pulmonary tissue is usually extensively diseased. Dangerous hemorrhages may result, and anaesthesia is in itself attended with danger in these cases. The uncertainty of the physical signs also contributes to the unsatisfactory results. Puncture of the bronchiectatic cavity with a trocar and drainage, incision and drainage, cauterization of the cavity, etc., are among the operative procedures advised. From the cases thus treated which have been so far reported, it would seem that under favorable conditions of life the outlook for patients with bronchiectasis is more favorable without operation than with it. Improvement of the technique of operations upon the lung may lead to better results.

The *postural* treatment of bronchiectasis is strongly recommended by Ewart (*Lancet*, 1901). While not regarding it as curative in advanced cases, he holds that no other treatment is so simple, so rational, and so effective. In a case so treated the relief afforded the patient was striking; the persistent pyrexia stopped, and the gushing character of the expectoration ceased. Ewart advises a continuous elevation of the foot of the bed of from twelve to fourteen inches. For brief periods a greater elevation may be resorted to with benefit.

Prognosis.—In so far as a cure is concerned the prognosis in any well-established case of bronchiectasis is bad. Except in rare cases no method of treatment at present employed is of avail in effecting a cure. Some of the more acute cases in young persons may, however, be cured. In the chronic cases our present methods of treatment can only relieve the distress of the affection and prolong life.

Aldred Scott Warthin.

BUXTON.—Buxton, situated in the Peak district of Derbyshire, England, at an elevation of about 1,000 feet above sea-level, is a pleasant and popular resort in the midst of beautiful scenery, frequented not only on account of its baths but as well on account of its fine bracing air and attractive situation. There are numerous and interesting excursions in the environs, of both scenic and historic interest. Chatsworth and Haddon Hall, for example, are within easy access.

Like Bath, which it also resembles in its waters, Buxton was known to the Romans; was visited by Mary, Queen of Scots; and has, for a very long period, maintained a high rank as a prosperous and popular health resort and spa. Unlike Bath, however, Buxton is a summer resort principally, the season extending from May to September. The air is cool and invigorating. For July, during a period of ten years' observation, the mean maximum temperature was 65.1° F., and the mean minimum 48.4° F. There is considerable rain, the yearly mean being 46.2 inches.

The waters of Buxton are of the *simple thermal* variety, of a natural temperature of 82° F. They are very weakly mineralized, slightly alkaline, soft, and contain in solution nitrogen gas in larger amounts than is present in other springs of the kind. The color of the water is of a "beautiful blue tint." Besides the simple thermal waters, there is a weak chalybeate water used both for drinking and as an application to the eyes. These waters are employed both for drinking and baths. There is a handsome "pump room" for drinking the waters and two bath establishments, one in which the

water is used at its natural temperature, and one in which the water is heated to any temperature desired. The usual varieties of baths are afforded here—douche, vapor, needle, and massage baths. There are also arrangements by which cripples are lowered into the waters.

The effects obtained by the use of thermal waters like those of Buxton are derived chiefly from their skilful application rather than from any mineral ingredients they possess, together with the careful ordering of one's habits of living in regard to diet, exercise, fresh air, and rest. Much of the benefit obtained by a visit to such spas as Buxton depends undoubtedly upon the change from one's usual routine of life and the pleasant surroundings of the spa.

The diseases and conditions which are benefited by the waters of Buxton are gout and gouty affections, rheumatism, diseases of the skin dependent upon a gouty diathesis. Joint stiffness and pain resulting from an attack of rheumatism are also relieved by the application of the hot water in the form of the douche massage, and the various baths which promote the absorption of morbid products and thus relieve the consequent disability.

The contraindications are: (a) febrile conditions; (b) advanced valvular disease of the heart, feeble or fatty heart or atheromatous vessels; (c) advanced disease of the kidneys; (d) extreme debility; (e) advanced disease of the lungs; (f) plethora, or an inclination thereto.

The general action of the waters is said to be stimulating, alterative, depurant, and diuretic. Upon the skin they exercise a detergent effect, improving its tone and function. Excretion of urea and uric acid is said to be increased. In beginning a course of baths there may follow certain nervous or circulatory disturbances, such as insomnia, giddiness, palpitation, and sometimes slight fever with increased pain and stiffness in the joints, but these effects soon pass away.

The natural baths, *i.e.*, at a temperature of 82°, are given from four to seven minutes, and the hot baths, those artificially heated, from four to fifteen minutes. After the bath the patient is wrapped in hot towels and dried by gentle rubbing. After the natural bath a brisk walk is recommended.

There are the usual means of amusement—theatre, concert-hall, reading-room, tennis, golf, conservatories, etc. The accommodations are good, consisting of numerous hotels and boarding-houses.

Buxton is reached in four and one-half hours from London.

Edward O. Otis.

CAMPHOR, POISONING BY.—An unwarranted belief in the innocuousness of camphor prevails in the community, referable, probably, to the safety with which it is used as an external domestic remedy for minor ailments and to its agreeable odor. This should not, however, blind the physician to its real and serious dangers when taken internally; for it may act as a poison either when eaten frequently in small quantities, as for headaches or colds, or when swallowed accidentally or intentionally once or more in large amount. It is true that fatal cases are very rare, but the symptoms are often most alarming, even when recovered from. The lethal dose of camphor is difficult to determine. The smallest dose known to have produced violent symptoms in an adult is 1.3 gm.; the largest dose known to have been recovered from is 15 gm. (Kunkel, Blyth). Camphorated liniments swallowed by mistake have frequently been the cause of severe cases of poisoning, the fact of the drug being in alcoholic solution allowing it to be absorbed and disseminated through the system more rapidly and in larger quantity than when swallowed in the solid form. The histories which I shall presently cite illustrate further the usual sequence of symptoms, and such relations as the early or late supervention of convulsions to the occurrence or absence of vomiting, this depending upon whether any large proportion of what was swallowed remained long in the stomach in a comparatively insoluble condition, or

was promptly taken into the circulation. Attention is also called to the statement that when camphor has been swallowed, what is absorbed undergoes such a transformation that the odor of it is not appreciable in the urine or feces (Kunkel); sometimes not even in the breath of the patient. Still, other authorities declare that the bodies of those dying smell strongly of the drug.

Full doses of camphor produce markedly exciting effects upon the brain and the medulla, especially when an alcoholic solution has been taken which favors rapid absorption. The earliest evidences of this stimulation are flushing of the face, a rapid succession of ideas, perhaps agreeable hallucinations, with a sense of lightness of motion and a desire to dance, in fact an intoxication. These manifestations are transient and may soon be followed by tonic cramps and epileptiform convulsions. To these may succeed sometimes paroxysmal tonic and clonic cramps with movements of rotation, followed by paralysis; or again deafness passing into sopor, coma, and death, the parts of the nervous system which are first excited being apparently finally paralyzed. The temperature is lowered, but the pulse and respiration vary (Brunton, Husemann). If the patient recovers, the memory is apt to be wanting for some hours. There are no characteristic lesions after death.

The following cases are fairly typical of poisoning by camphor: Davies reports being called at 3 A.M. to a child of two years and eight months, who had swallowed solid camphor. He found it pale, with blue lips, a rapid pulse, and suffering from severe convulsions. Vomiting was induced and the ejecta smelled strongly of camphor. The child soon recovered in part from its condition of collapse, but the convulsions continued, and in the intervals the patient was semicomatose. A stomach-pump was then used and the stomach washed out with warm water, procuring some relief. In five hours castor oil was given, also bromide of potassium, three grains every three hours. Still no improvement; the convulsions continued all night and the child died at 9 A.M. of the next day. The amount of camphor taken was probably half a drachm. From its being solid the stomach-pump could not act upon it effectively.

Craig reports that a man who was a hypochondriac ate about three drachms of pure camphor. About half an hour after swallowing it he was seized with giddiness and nausea, staggered on rising and seemed likely to fall. Still he was unable to vomit, and was relieved by drinking some water. He was free from pain, and lay down with a drowsy ringing in the ears. In three-quarters of an hour the giddiness and nausea had gone, but he felt as if he had been taken from his feet and were being carried through the air. He sat down at the dinner table, but became suddenly unconscious. He had general convulsions, which soon ceased, and the reporter says there was no deviation of the eyeballs, pupils equal and small and not reacting to light, knee-jerks exaggerated; breathing rapid, cyanosis followed by pallor. He was not unconscious for over five minutes. There was no odor of camphor in the breath. About two hours and a half after taking the camphor he vomited copiously, and brought up no blood and some camphor. There was no retention of urine. His memory was affected for an hour after other symptoms had disappeared.

Honman reports the case of a girl of eighteen, to whom he was called at 11 A.M. She was in the habit of eating camphor. He found her unconscious and irritable, with dilated pupils, cold extremities, pale face, epigastrium sensitive to pressure, pulse thready and uncountable, and the breath smelling distinctly of camphor. The stomach was washed out after an unsuccessful attempt to produce vomiting by sulphate of zinc. Ether was given subcutaneously with immediate improvement. It was learned that she had had camphor in her hand, and had offered it to her roommate at bedtime. She had vomited during the night and had taken brandy and water about 8 A.M. Convulsive movements now began and extended from the lower extremities to the body and upper limbs. The temperature rose to 100.3° F., and the pupils were

dilated. She died at about 3 A.M. the next day. At the autopsy the only finding attributed to camphor poisoning was a high degree of congestion of the vessels of the dura mater and surfaces of the brain. The government analyst reported a small quantity of camphor in the stomach, but it is observed that none of the ejecta or dejecta had been saved prior to the doctor's arrival at 11 A.M.

In regard to the treatment of poisoning by camphor, the most important precept laid down is the earliest possible emptying of the stomach by tube, stomach-pump, or emetic. Hypodermic injections of brandy or ether may be used, with perhaps the alternate hot and cold douche.

J. Haven Emerson.

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CANTHARIDES, POISONING BY.—The poisonous action of this drug is ascribed chiefly to the proximate principle *cantharidin*, which is from twenty-five to thirty times as active as the powder. As the unassayed powder or the tincture is the form in which it is most apt to have been taken, it is difficult to determine the fatal dose of cantharidin. Blyth states that a young woman died from twenty-five grains of the powder, probably equal to one grain of cantharidin, while the smallest dose of the tincture known to be fatal (Taylor) is an ounce, equivalent to gr. $\frac{3}{16}$ of the proximate principle. Poisonous effects may also follow from external applications of the drug, in which they result from absorption, especially in feeble persons and children. Blyth says that the popular idea of the influence of cantharides as an aphrodisiac holds good only as to the entire cantharides, and not as to cantharidin, and he considers it probable that cantharidin is not the only proximate principle in the insect. It is also stated that cantharides may be eaten with impunity by fowls, while the flesh of the latter may produce symptoms of poisoning if eaten by human beings. Ogier tells us that a fatal result may follow poisoning by this drug after as long an interval as twenty-four hours; also that proof of the cause of death may be found in the presence in the intestine of minute glistening particles of the insect. Fatal cases are rare.

The symptoms due to poisonous doses are given as follows by Husemann, Kunkel, and Blyth: They are shown in disturbances of respiration and in convulsions from involvement of the nervous system, often with headache, dizziness, stupor, and delirium. In the alimentary canal there appear at once burning in the mouth and throat followed by pain on swallowing, salivation, vomiting, and diarrhoea, while there develop intense irritation, pain, and a condition of inflammation of the kidneys and urinary passages, in consequence of which occur in the urine albumin, casts, pus, and blood, with catarrh and croupous deposits from the vesical mucous membrane. These are associated with strangury, dysuria, painful erections, and priapism. Sometimes pregnant women have aborted.

The following fatal case is reported by Lhôte and Vibert. A man of about sixty took a quantity of cantharidin, estimated at about 75 cgm. He died twelve to fourteen hours afterward, the symptoms presented not being accurately known. Autopsy four days post mortem. The lungs were much congested; there was a little froth in the bronchi. Stomach empty; mucosa actively congested. Kidneys large, turgid, and extremely congested; several large sanguineous effusions under the capsule; cortical and medullary substances gorged with blood and the mucosa of the calices and pelvis strongly injected. Bladder contained 4-5 c.c. of bloody urine; mucosa strongly congested and of an intense red; no

ulcerations but many ecchymoses. Mucosa of the urethra likewise congested. On microscopical examination of the kidneys the glomeruli were found detached from their capsules, and separated from them by an exudate, in the midst of which were seen at certain points numerous round, nucleated cells. In the convoluted tubes the epithelial cells appeared glued together; they filled and distended the tubes. A material extracted from the viscera produced upon animals the effects of cantharidin, and its chemical reactions were characteristic of that substance.

The treatment of poisoning by cantharides must be symptomatic. The stomach should be evacuated, the stomach-pump or tube being used for the purpose if the mouth and throat are not inflamed; if they are inflamed, apomorphine should be injected hypodermically or an emetic should be given. Opium and hot sitz baths should be used to allay pain and strangury, and water and mucilaginous drinks given freely, but fats and oils are to be avoided.

J. Haven Emerson.

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CAROTID GLAND.—(Synonyms: Ganglion intercaroticum; Glandula carotica; Glomeruli arteriosi intercarotici; Nodulus intercaroticus.)

This little-known organ lies in the bifurcation of the common carotid artery, generally near the posterior side of the internal carotid just as it comes off the main trunk. In size it averages 5 mm. in length, 2 to 5 mm. in thickness, and 3 mm. in breadth (Gomez), varying considerably. Because of its great vascularity the color is pink. For some time it was thought to be an epithelial organ developed similarly to the thyroid and thymus

in its formation consists of a cellular thickening of the external posterior portion of the periphery of the embryonal carotid. At this time the cells, of epithelioid type, are not distinguishable from the cells of the vessel wall itself, and the gland anlage is recognized merely as a thickening of the cell mass at this point. This entire nodule is surrounded by the adventitia, and over it run nerve bundles from the vagus and cervical sympathetic. Very early in its development capillary vessels derived from the common carotid at its bifurcation enter the cell mass, and soon form glomerule-like collections, which with the rapidly increasing cell growth soon distinguish the gland from the vessel. It increases in size until the third decade.

In the adult the carotid gland shows a lobular structure. From the connective-tissue capsule, bands pass into the organ, carrying many vessels and nerves, and dividing it into lobules, which vary in number from three to twelve. In turn the lobules are composed of small "cell balls," which really form the unit of its structure. These consist of a glomerule-like tuft of capillaries that unite to form a vein. Surrounding the capillaries are the cells of the organ, arranged in cords or trabeculae, although this arrangement is not at all evident in ordinary preparations. The number of cells about individual vessels varies greatly; sometimes there is quite a wall of epithelioid cells, with finely granular cytoplasm, oval nucleus, and a nucleolus, but often there is but a single layer of cells about a vessel, or the vessels may be separated merely by a loose reticular interstitial connective tissue. In this reticular tissue are frequently single cells of the same type. Often the parenchyma cells show a considerable degree of vacuolization, particularly in the old. According to Gomez there are two types of parenchyma cells, differing in the amount of chromatin and the size of the nucleus. It is said that with age the typical structure becomes less and less evident, accompanied by more or less disappearance of these special cells, and increase of the fibrous tissue. The structure of the carotid gland is quite similar to that of the coccygeal gland.

The function of the carotid gland is altogether unknown. It seems to have been the subject of but little investigation except by histopathologists. It is undoubtedly closely related to the sympathetic nervous system, as shown by the number of ganglion cells and nerve fibres from the cervical ganglia, and by the presence of the same cells with affinity for chromic acid and its

salts, the so-called "chromophile" cells that are found also in the sympathetic glands, adrenal, and coccygeal gland. In the few recorded cases of tumors of this gland there have been no symptoms that could be considered indicative of any function, and the unilateral resection of the gland in these cases has been followed by no symptoms whatever. Extracts from the gland are said to raise the blood pressure greatly.

PATHOLOGY.—Except for tumor growths there seem to be few records of pathological alterations in this organ, probably because it escapes observation through its location and its minute

size. Gomez found that it shows a sclerosis in direct proportion to the amount of sclerosis in the carotid artery, whether senile or syphilitic; in acute infectious diseases it rarely shows parenchymatous degeneration; no other lesions were observed in some fifty autopsies.

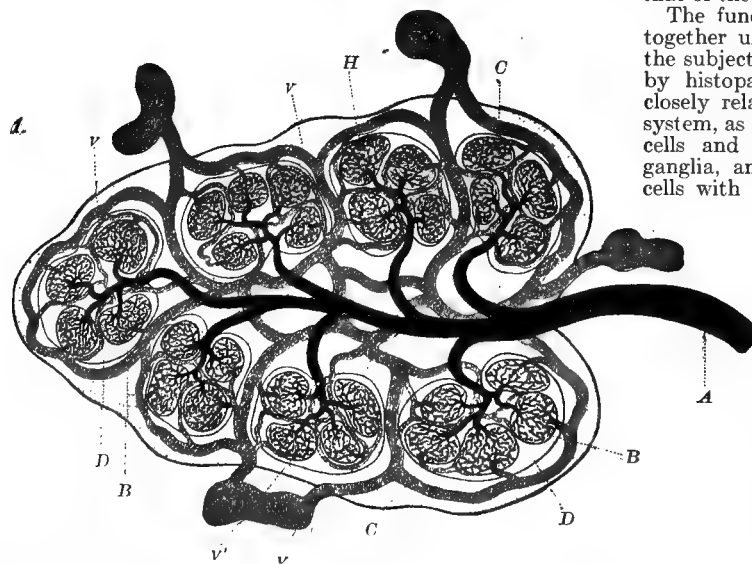


FIG. 5133.—Scheme of Circulation and Structure of the Carotid Gland, showing its Glomerule-like Character. (After Schaper.) A, Principal artery with V, corresponding vein; B, balls of cells; C, capillary networks; D, secondary nodules; H, hilus; v, v', smaller veins.

from the branchial clefts, but further study showed it to be of entirely different origin and nature. Its embryonal origin is later than the thyroid and thymus, and it is in no way related to them, for it arises directly from the primary vascular anlage, and therefore is not an epithelial, but a perithelial, structure. The first step

Keene and Funke were able to collect in the literature from 1891 to 1906 reports of 27 cases of tumors of the carotid gland which had been operated upon, besides two observed at autopsy. Of these 27 cases, 17 were

observed. They are commonly localized by a well-defined capsule, divided by fibrous septa, and the color is extremely variable. The tumor is rather firmly fixed, because of its relation to the carotids, and for the same reason it frequently transmits pulsation which has led to a diagnosis of aneurism. In the other cases tuberculous cervical glands and thyroid tumor have been suspected. The diagnosis has usually been made only at operation, when the location of the tumor in the bifurcation of the carotid is quite characteristic. Clinically this relation to the artery, the slow growth in the early history, the elastic consistence, and the scanty subjective symptoms are suggestive features.

The malignant tumors of the carotid gland testify to its origin in the perithelium, for they form quite typical peritheliomas. The tumor is generally highly vascular, and about the capillaries are layers of epithelioid cells, with a strongly staining oval nucleus, and considerable finely granular cytoplasm. The thickness of these walls seems limited by distance from blood supply, and the perithelial cells tend to form cords with central spaces lined solely by the tumor cells. The lobular structure of the gland is retained, as well as its richness in vessels and nerves.

H. Gideon Wells.

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CHYLOTHORAX.—This is a condition in which the pleural cavity contains chyle, due to a break in the continuity of the wall of the thoracic duct or its branches, or to some pathological condition of their walls whereby the contents may be transuded into the pleural cavity. Other writers give the name chyloform to those fluid exudates, in the pleural cavity, which contain fat in smaller amount than is found in the cases belonging to the class first mentioned. Furthermore, as these so-called chyloform fluids accompany tumors of the pleura in many cases, these writers believe that the fat comes from a fatty degeneration of the tumor cells. In a third class of cases the fat of the pleural fluid is supposed to result from lipæmia. In the latter cases the amount of fat contained in the fluid in the pleural cavity is small.

As stated, true chylothorax results from some definite lesion of the thoracic duct or its branches; but since lesions of this organ are not common, and since all lesions of the duct are not followed by chylothorax, the presence of chyle in the pleural cavity is an unusual condition.

Many of the older writers confused chylothorax with empyema or with the fibrinous exudates accompanying certain cases of pleuritis, and consequently some of the cases reported by these men, when studied carefully now, are found to be of a nature different from true chylothorax. It being assumed that this statement is correct, it appears that only forty-seven cases of genuine chylothorax have been reported, besides about fifteen others which are doubtful cases.

ETIOLOGY.—In the undoubted cases the age varied from 2 to 62. Two cases occurred in patients under 10 years of age; 8 in patients from 11 to 20; 7 from 31 to 40; 8 from 41 to 50; 3 from 51 to 60, and 2 after 60. From

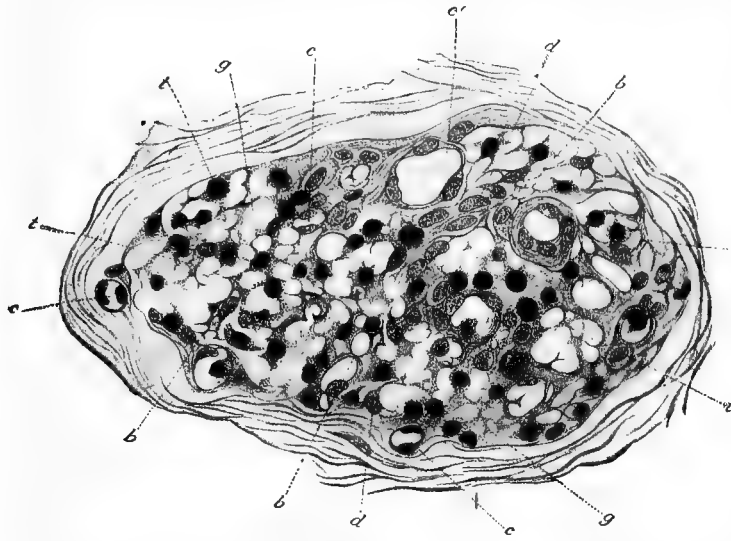


FIG. 5134.—Section of a Lobule of the Carotid Gland. $\times 520$. From a man fifty years of age. (After Schaper.) a, Smallest arteriole; b, connective-tissue reticulum; c, capillaries; d, nuclei of stroma; g, protoplasmic network; t, nuclei of gland cells.

in patients from 13 to 35 years of age, 7 between 36 and 50, and only 2 after 50 years of age; there were 14 in males and 15 in females. These tumors are characterized by their location in the crotch of the carotid, with which they are so intimately connected that the vessel usually must be ligated and cut across in removal of the tumor. Some of the tumors are quite benign in character, but frequently they are very malignant; in

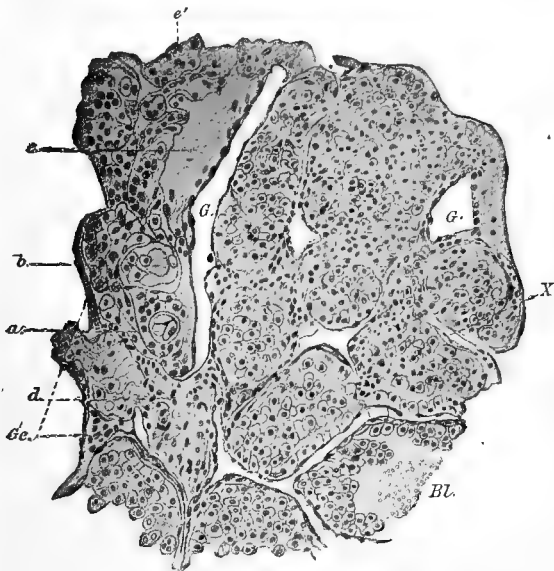


FIG. 5135.—Perithelial Tumor of the Carotid Gland. (After Paltauf.) G, Vessels; Bl, blood extravasation; a, hyaline degeneration of cells; b, hyaline degeneration; c, hyaline masses.

five cases metastasis in the regional lymph glands was observed, and in several of the patients operated upon a speedy recurrence followed. They usually produce few subjective symptoms, although occasionally headache, hoarseness, and narrowing of the pupil have been

this it can be seen that the greatest number of cases occur between the ages of 11 and 51. This is explained by the fact that individuals between these ages are more exposed to injuries, or are more subject to new growths—conditions which are frequent causes of chylothorax.

In 41 of the undoubted cases in which the sex was given, 31 were males and 10 were females.

Chylothorax may result from obstruction to the flow of chyle through the thoracic duct, due to pressure from without by new growths or by tuberculous lymph nodes in the mediastinum. The obstruction may also be due to occlusion of the lumen by secondary new growths or to the presence of thrombi in the duct or in the left subclavian vein—in the latter case obstructing the mouth of the duct. Finally, it may be due to the presence of filaria. In other cases chylothorax results from pathological changes in the duct wall or from traumatic injuries to its walls.

Of the undoubted cases 16 resulted from injury to the chest; 9 from pressure exerted upon the duct by new growths outside the duct or by tuberculous lymph nodes; 9 from secondary growths in the duct; 4 from thrombosis of the left subclavian vein; 2 from proliferating lymphangitis; 2 from aneurism-like dilatations of the duct, and 1 each from the following: thrombosis of the duct, operation for removal of carcinomatous lymph nodes of the neck, obstruction to the radicles of the duct from inflammatory thickenings in the mesentery, mitral disease, and filaria. All of these causes either produce a break in the continuity of the endothelial lining of the duct or put the endothelial cells under such abnormal conditions that their nutrition is impaired, and consequently they allow the transudation of the chyle.

SYMPTOMATOLOGY.—The symptoms of chylothorax which result directly from this condition are not characteristic. For the most part they resemble those of hydrothorax or a pleuritic effusion. In most cases the chief, and sometimes the only, symptom is a gradually increasing dyspnoea. In fatal cases this may be accompanied by a rapidly progressing emaciation, although the patient may have a good appetite and may eat well. A few of the patients complain of pain in the affected side if the chylothorax is unilateral, and of a general, indefinite, dull pain in the chest if the condition is bilateral. On inspection lagging of the affected side will be noticed and the intercostal spaces will be more or less obliterated. If the quantity of fluid is large, the heart may be displaced away from the fluid. Palpation reveals a lessened or entirely absent vocal fremitus, depending upon the amount of fluid present. Percussion always gives a dull note on the affected side of the chest, both laterally and behind, the line of dulness being higher in front and lower in the back when the patient sits up, and reversed when the patient lies down.

In seventeen of the forty-seven cases chylothorax was accompanied by chylous ascites, and in one instance by chylopericardium. In one case there was chyluria, and in another milky diarrhoea.

The symptoms referable to other organs are usually due to the same pathological alterations as those which have brought about the chylothorax. In cases of external injury to the duct very few symptoms other than those mentioned appear.

DIAGNOSIS.—The only evidence upon which a positive diagnosis of chylothorax can be based is that afforded by an examination of the fluid. This fluid, as withdrawn by an aspirator, is usually semitranslucent, milky, and opalescent. Its specific gravity is 1.020 in most cases. If allowed to stand, the fluid separates into two layers, an upper, slightly more yellow in color, and resembling cream in consistence, and a lower one, watery in character. If the whole is well shaken and extracted with ether or treated with sodium or potassium hydrate, the fluid becomes clear and loses its milkiness. Chemical examination of the fluid shows that from ninety to ninety-nine per cent. is water. Of the solids, the fat varies from 0.02 to 0.92 per cent.; salts and albumins, and sometimes a small amount of sugar, forming the remainder.

PROGNOSIS.—In many cases the prognosis of chylothorax is good. In those which are due to obstruction, the anastomoses of the thoracic duct may do compensatory work, and thus the condition may be relieved. In cases due to injury to the duct from external causes, proper treatment frequently brings about a cure.

TREATMENT.—For those cases in which the chylothorax is due to some chronic obstruction, aspiration of the fluid, accompanied by rest and nourishing food, is about all that can be done. Cases due to injuries of the chest are treated in a similar manner.

In cases due to injury inflicted during an operation for the removal of carcinomatous or tuberculous lymph nodes in the neck, the duct may be ligated, resected, or packed, all of which procedures have been used.

Frederick A. Baldwin

Most of the literature of chylothorax is given by Bargebuhr, *Deutsches Archiv für klinische Medizin*, 1895, liv., 410, and by Shaw, *Journal of Pathology and Bacteriology*, 1900, vi., 339.

COLON, CONGENITAL DILATATION OF.—Synonyms: Idiopathic dilatation of the colon; Dilatation and hypertrophy of the colon; Megacolon congenitum; Hirschsprung's disease; Congenital inertness of the colon; Neuropathic dilatation and hypertrophy of the colon.

Historical.—According to Nothnagel this disease has been described for over fifty years. In 1880 the condition was carefully studied by Hirschsprung, of Copenhagen, so that in Germany the disease is generally known by his name. Kredel in 1904 collected seventy cases from the literature, and recently Hawkins (*British Medical Journal*, March 2d, 1907, p. 477) has described nine cases ranging in age from three weeks to forty-eight years. Quite a literature of the subject has accumulated, the most important contributions being those of Hirschsprung, Concetti, Gourévitch, Netter, Ibrahim, Marfan, Kredel, Hale White, Fenwick, Richardson, Treves, and Hawkins.

Definition.—The condition may be perhaps best defined as a dilatation and hypertrophy of the lower segment of the colon or sigmoid flexure. It is not due to any mechanical obstruction, but probably to congenital deficiency in the innervation of the bowel. In most cases the dilatation depends upon a paralytic condition of the bowel, but in rare instances a condition of spasm has been found. A few of the cases which have been recorded as examples of this condition are really instances of faecal impaction leading to great dilatation of the colon behind the impacted mass.

Symptoms.—The condition occurs more frequently in males than in females, at all ages, and the cases may be divided into the following groups: I. Cases in which at birth or the first days of life there are obstruction and distention of the abdomen. II. Cases in which the condition develops a few months after birth, mostly at the time of weaning or of adding solid food to the diet. III. Those that develop some years after birth. IV. Cases in which the symptoms develop in late adult life, usually between forty-five and fifty-five years of age.

Group I.—In an infant born with no evident abnormality the condition is revealed by the fact that there is no spontaneous passage of meconium. On examination with the finger no mechanical obstruction can be found. Enemata bring away a small quantity of meconium. The child is restless, sleeps poorly, has no defecation without assistance; then distention of the abdomen appears. The abdomen becomes hard, its skin covered by dilated veins, and there is perhaps also some oedema. Dyspnoea and cyanosis may supervene. If irrigations are given, only the water returns, but following the insertion of the finger into the rectum, especially if massage of the abdomen is practised at the same time, a large quantity of meconium or faeces is passed. As the abdomen diminishes in size, the child's general condition improves, it begins to take its feedings which formerly were refused, the cyanosis diminishes, and the baby is comparatively well. Later on, the whole series

of symptoms is repeated time and time again until death ensues. The cause of death is either failure of the respiratory organs, inanition, or chronic intoxication from the absorption of decomposition products from the intestine. If intoxication exists there are apt to be coma, convulsions, and meningeal symptoms. This group of cases comprises those that are designated Megacolon congenitum.

Group II.—These are cases in which during early infancy the general health was good and the function of the bowel either normal or there was only slight constipation. At the time of weaning or of beginning solid food, obstinate constipation appears, then distention of the abdomen and the development of the balloon shape to the trunk. The children then develop severe cachexia from the absorption of toxic products from the intestine, and die. They have all the symptoms of Group I. At autopsy these cases are found to have ulcerative processes of the mucous membrane of the large intestine and frequently submucous abscesses.

Group III.—After a history of constipation for a number of years the characteristic symptoms develop and the course of the disease is much the same as outlined above. To this class belong the so-called "balloon men" in whom the distention of the abdomen is so enormous as to make the lower part of the trunk almost globular.

Group IV.—These cases seem to be acquired late in life. They develop the full set of symptoms and the physical signs which will be described below. A careful inquiry in the history will reveal that there has always been more or less trouble in securing voluntary evacuation of the bowel.

The general picture of the condition is very lucidly given by Hawkins as follows: "(1) A history of constipation from birth—compatible, however, with good health until the final stage, the first sign of failure being often loss of weight. (2) A constipation which often alternates with diarrhoea and which at its worst is unlike that of obstruction, since flatus is often passed and faecal matter can be drained away through a rigid rectal tube. (3) Abdominal enlargement, variable or constant, often asymmetrical, with prominence in the left iliac region; the abdomen, though distended, is seldom tense and often surprisingly flaccid, and it rarely presents any impairment of resonance. (4) Slow alterations in shape, especially in the left iliac region, observable only with patience—unlike the tense peristalsis seen in real obstruction. (5) Absence or rarity of pain and vomiting."

The abdomen is often enormously distended. The lower colon and sigmoid may fill nearly the whole abdomen, displacing the liver upward and forming either a prominence resembling an extraordinary dilatation of the stomach or else looped upon itself so as to form two huge pipe-like prominences like a great inverted U extending vertically or obliquely up to the thorax. The dilated colon may measure two feet in circumference. When the dilatation is not of the sigmoid flexure it is usually near it. There are dyspeptic symptoms, especially colicky pains, and there is malnutrition. Frequently purgatives are effective; at other times they are of no value. It is characteristic that by inserting a firm catheter or drainage tube into the rectum, or even by passage of the finger, there will be secured a movement of the bowel and a discharge of gas. Roser says: "The introduced finger reveals a considerable narrowing; but above this is a large, sacciform distention." Göppert writes: "The finger passes through a normal rectum to a point 6 or 7 cm. above the anus, somewhat under the promontory (case, child of five weeks); on slight flexion the first phalanx of the inserted finger passes into a hollow space. If the finger is extended and withdrawn there occurs a passage of gas and faeces and then with great ructus the abdomen collapses."

Physical Signs.—The distended abdomen is tympanitic throughout nearly its whole extent. The splenic dullness is obliterated, the hepatic dullness diminished, and

the liver cannot be felt. The heart is displaced upward, and this gives rise to palpitation. There is dyspnoea and there may be cyanosis, both of these symptoms being due to the pressure upward against the diaphragm. Usually neither coils of intestine nor peristaltic movements are visible. In very rare cases there is œdema of the legs, scrotum, and penis, and also albuminuria, all of these symptoms being dependent upon pressure.

Complications are the results of pressure. There may be dyspnoea, rarely hydronephrosis, and occasionally œdema of the lower extremities. Tetany has been known to occur, and, as in the case of acute dilatation of the stomach, it requires immediate operation.

Pathology.—Necropsies have uniformly shown an enormous distention of the colon, varying from fifteen to thirty inches in circumference and extending from the upper part of the rectum a variable distance along the colon toward or to the cæcum. There is always thickening of the muscular wall of the colon, which may reach a width of one-fourth of an inch. The bowel is thus rendered unusually rigid and shows little tendency to collapse on puncture. The mucous membrane is usually inflamed and at times studded with ulcerations. In a few cases submucous abscesses are present. The small intestine is never dilated. The distended bowel contains semifluid faeces and a great deal of gas. Strictures have not been found. It is evident that the thickening of the muscular coat is a compensatory hypertrophy, and this hypertrophy affects both layers.

Pathogenesis.—The origin of the affection is not absolutely determined. Hirschsprung believed the condition to be a congenital primary dilatation and hypertrophy of the large intestine. Marfan regards it as secondary to a congenital anomaly in the form of the sigmoid flexure. Anatomical kinking or valve formation has been advanced as explaining the condition, but the dilatation, as shown by Hawkins, begins gradually in the lower part of the pelvic colon, just above where it joins the rectum. The best explanation of the condition for all the groups of cases, advanced by Hawkins, is that it depends upon a congenital nervous defect in the lower part of the colon. The condition is almost always paralytic. One exceptional case of spastic contraction is that of Hilton Fagge (1880), reported by Gee. In this case there was a spastic condition below the immensely dilated pelvic colon; but the contraction was not very tight, easily admitting the index finger.

Diagnosis.—The condition must be distinguished from intestinal obstruction and from the simple non-dilating constipation. A careful comparison of the symptoms should prevent one mistaking the condition for intestinal obstruction. In its early stages there may be difficulty, however, in making the diagnosis from simple constipation and also, as Hawkins emphasizes, in recognizing the point at which the case becomes surgical. It is very important to make an early diagnosis, since there is a stage in some cases when cure is possible by surgical means.

Prognosis.—The prognosis is very bad, as nearly all the patients die if not operated upon. Many children suffering with this condition die early with obstinate constipation and extreme emaciation following repeated attacks of apparent intestinal occlusion. Other patients attain a greater age, but in these the symptoms have begun late. A few persons who were operated upon have recovered, and this really holds out the only hope after the condition has fully developed.

Treatment.—The treatment by medical measures has hitherto been unsatisfactory, and even the surgical treatment has not been very successful. Cathartics may be effective for a short time, but soon lose their power and add to the difficulties of the situation. Irrigation and the use of firm rectal tubes are the most effective measures. Faradization of the abdomen is an aid, but massage is dangerous, since, if the colon is ulcerated—as obtains in some cases—rupture might result.

Operative Measures.—Tapping the colon is dangerous and might easily lead to leakage and peritonitis, though the transverse colon was punctured in Cheadle's case and the patient recovered. An artificial anus was made in the cases of Osler and of Gwynne and the patients recovered. Parts of the colon have been excised successfully by Treves and Maurice Richardson. In the latter's case, however, although the sigmoid flexure was excised, a new hypertrophied sigmoid flexure was formed, large enough to fill the lower abdomen, in fifteen months. According to Hawkins, colotomy is useless: excision of any part of the colon should never be permitted; and the best result with the greatest safety is probably given by anastomosis of the iliac and pelvic colon coupled with fixation of the dilated pelvic loop. Where this is not possible, probably the next best course would be to open the bowel above the dilatation, wash out the dilated part, and let the faeces pass for some time through the artificial anus so as to give rest to the affected part. *Linnæus E. La Féra.*

CONTREXÉVILLE.—Contrexéville, a spa of European celebrity, is situated in the Vosges Mountains southeast from Paris at a distance of about 230 miles from that city. The village and springs lie in a valley below the level of the surrounding country, at an altitude of 1,100 feet above sea-level. The "season" at which this resort is frequented extends from May 20th to about the first of October, and the climate at this time is temperate, with more or less of the characteristics of a mountain resort; namely, sudden changes of temperature and cool or cold mornings and evenings, so that one must be provided with suitable clothing for protection against these sudden changes. There is considerable rain and cloud.

The character of the waters is earthy or calcareous, sulphate and carbonate of lime being the chief constituents, with minute quantities of the sulphates or carbonates of sodium, magnesium, lithium, and iron, and the chlorides of potassium and sodium.

It is a clear, still, almost tasteless water, with a temperature of 52° F. The chief and most important method of using these waters is by drinking, although baths, douches, and massage are also employed as adjuvants to their internal use; douches for the loins being a common method of application.

The special diseases for which these waters are used and success in which has made Contrexéville so famous, are those of the urinary organs, particularly gravel and renal calculous diseases, and the conditions resulting therefrom: pyelitis, pyelonephritis, and chronic cystitis. Gout and gouty conditions when dependent upon a supposed excess of uric acid in the system are also greatly relieved, and so also are gallstones, congestion of the liver, dyspepsia, diabetic gout, and such skin diseases as eczema, acne, or psoriasis, when the underlying cause is considered to be an excess of uric acid in the system. Nocturnal incontinence of urine in children is said to be benefited or cured by their use.

The principle of the treatment is internal lavage, the rapid passage of a large amount of water through the system, dissolving and carrying away toxic substances, and mechanically removing from the urinary passages sand, gravel, mucus, purulent secretions, etc. To accomplish these results, from one to six quarts of water are drunk daily, mostly in the morning from 4:30 to 9; some patients exceed this amount by even to eight or ten quarts daily.

The immediate effect of the ingestion of this large amount of water is diuretic and aperient; the purgative effect occurs soon after taking of the water and does not generally recur during the day. Drinking the water in the latter part of the day is not, as a rule, practised. The purgative effect sometimes fails and then recourse is had to a more definitely purgative water (Source Souveraine) or to a purgative; generally, however, this not necessary.

The general plan of the patient's day is as follows:

Taking the water in the morning from 4:30 to 9, the favorite time being about 7 A.M. Between glasses a short walk is taken. At 10 a substantial breakfast is eaten. Excursions, outdoor games, walks, etc., follow, and at 6 o'clock dinner is served. After dinner on certain days there are concerts and other amusements, and at 10 P.M. most of the invalids retire.

The contraindications are, in general, such conditions as are unsuitable for any spa cure, and especially the following: cancer and tuberculosis of the kidneys; cases of pyelitis and renal gravel with a continuously considerable amount of albumin in the urine; large calculi in the pelvis of the kidney; stone in the bladder; vesical paralysis with retention of urine; vesical tumors; extensive hypertrophy of the prostate; acute cystitis; cases of hepatic cirrhosis; cases of gout when an acute attack seems imminent or has just been checked by treatment; cases of diabetes with very large amounts of sugar, or complicated by nephritis or cirrhosis.

There are several springs, but the main one is the Pavilion, the waters of which are exported in large quantities.

The bath establishment possesses a fine park with gardens and pleasure grounds, and connecting with a central dome-shaped building, in which is the Pavilion Spring, are glass-covered galleries with shops, so that one can take the waters in rainy weather without being exposed. There are theatres, a casino, and many facilities for amusement and exercise. There are also pleasant drives and walks in the hills about. The hotels are good and of varying prices, and there are villas, furnished houses and rooms to be obtained.

"The life is certainly monotonous and a trifle depressing," says Burney Yeo, but he adds, "the treatment is the end and object of being there," and in the maladies for which these waters are peculiarly applicable one can be assured of so much benefit that he can endure this monotony with equanimity when he finds himself recovering or greatly improving. *Edward O. Otis.*

CORN.—*Synonyms:* Clavus, Clou, or Cor.

Definition.—A corn is a localized hypertrophy of the epidermis, generally found on the feet, and due to pressure or the intermittent friction of ill-fitting shoes. Corns are classified as hard and soft.

Hard corns are usually found on the outer surface of the little toe; or over the head of the first or fifth metatarsal bones; or over the head of the phalanges of the other toes, especially in people who are prone to hammer-toes.

Soft corns occur between the toes.

Hard corns are largely due to shoes that are high-heeled, or too small, or misshapen; occasionally a shoe that is too large may, by intermittent friction, produce a corn.

A *hard* corn is a conical, wedge-like mass of hardened epithelium which is pressed down on the underlying papillæ; and these, in consequence of the pressure, atrophy and form a cup-shaped depression; at the same time the neighboring papillæ hypertrophy, the subcutaneous fat disappears, and a small bursa may form. It is this central hard and horny plug which differentiates a corn from a mere callosity.

Soft corns, between the toes, are spongy and vascular; they are covered with a macerated epithelium; owing to the absorption of perspiration they are white and sodden, and often present deep fissures, and are very painful. They are found more often in the summer, and in the wearers of patent-leather shoes.

In addition to the pain and discomfort (which can be considerable) caused by corns, they occasionally give rise to complications such as suppuration under the corn or erysipelas or gangrene due to home or other amateur treatment with an infected instrument. Mere cutting of a corn may be attended with gangrene in old people.

Treatment.—The treatment of corns consists in remov-

ing the cause, and keeping it removed. Proper attention must be paid to the shoes; these should not be made of patent-leather, they should not be too large or too small, the inner border should be straight, the heels low, and the toes rounded and not pointed. If this matter were attended to and persevered in, further treatment would, as a rule, be unnecessary. A *hard* corn, which is not inflamed, should be soaked in hot water, the top should be carefully pared off, and then a drop or two of glacial acetic acid, or nitric acid, or a solution of nitrate of silver (gr. x.-xxx. to 3j.) should be applied. Within a few days the hardened epidermis can be peeled off, and the treatment repeated. This can be continued as often as necessary, but usually three or four applications are sufficient. In place of the above, the corn after being softened with hot water may be painted with the following solution (from Crocker):

R̄ Acidi salicylici, gr. xv.
Extracti cannabidis indicæ, gr. viij.
Alcoholis, ℥ xv.
Ætheris, ℥ xl.
Collodii flexilis, ℥ lxxv.

Misce.

Sig. To be painted on with a brush three times a day, for a week.

Most of the corn cures on the market contain salicylic acid. A corn plaster of salicylic acid or felt may also be worn; it should be circular, with a hole in the centre. There should be no attempt to cut out the corn. It must be remembered that these applications do not remove the cause, and hence should be secondary only to proper shoes, etc.

If the toe is much deformed, amputation may be necessary, or the toes may have to be straightened by splints or by a tenotomy. If the corn is inflamed, rest is indicated, with the application of lead-and-opium solution, and as soon as pus forms it should be let out.

For *soft* corns, in addition to properly fitting shoes (see above), the feet should be frequently cleansed, preferably by washing with ethereal soap; they should be kept as dry as possible; socks and stockings and shoes should be frequently changed; a dusting powder of starch and zinc oxide may be used, or belladonna liniment or spirits of camphor may be painted on at night, cotton wool being worn between the toes during the day. Intractable soft corns may be treated in the manner recommended by A. M. Phelps (*Transactions of the American Orthopedic Association*, Vol. VI., 237) the adjacent sides of the two toes are freshened, and then stitched together, thus making one toe of them; by this method the usefulness of the foot is not impaired as is the case in amputation. R. J. E. Scott.

CUTI-REACTION IN TUBERCULOSIS.—Von Pirquet of Vienna has used tuberculin applied to skin scarification to determine whether the subject was tuberculous. A local irritation—hyperæmia—results, being marked in the tuberculous, slight in the non-tuberculous. There is a local leucocytosis accompanying the hyperæmia.

There is a wide range of difference in the reaction when tuberculin is thus directly applied, dependent upon the degree of infection, its virulence, and length of the infection. It appears that none of the toxin reaches the circulation. Febrile reactions do not follow, and nothing remains but a papule, which differs distinctively from the control scratch, and a local swelling with hyperæmia. In seven hundred inoculations v. Pirquet observed but three cases in which there was a rise of temperature. The inoculations, however, were not always without systemic effect. Second inoculations were usually followed by an accelerated and intensified reaction. Frequently the initial inoculation was negative, but subsequent ones proved positive. In several of these cases when autopsies were possible, caseated foci were plainly demonstrated. Von Pirquet declares that

the skin inoculation of tuberculin stimulates the antibodies.

The papule is about 10 mm. in diameter; when it is larger it occurs in hypersensitive subjects and in cases of scrofula, bone, and joint tuberculosis. Occasionally cases will be found in which the reaction is difficult to determine; these should be considered as negative results. The color of the reaction is a bright red, gradually fading into a slightly pigmented spot which may remain visible for several weeks. Cachectic children often present a very slight hyperæmia or cyanotic discoloration. In these cases the reaction will be entirely free from exudation.

The papule begins to show itself usually within twenty-four hours after the inoculation, the efflorescence reaching its maximum after twenty-four to forty-eight hours. In the case of older children the reaction may not appear until after forty-eight hours.

This method of diagnosing tuberculosis is especially applicable to children in institutions and hospitals and offers a harmless means, v. Pirquet claims, of determining the disease in its incipency, thus affording the best means for successful treatment. As a diagnostic agent the skin inoculation of tuberculin is of positive value in early infancy only—between the ages of one and two years. In older children and in adults it possesses merely a negative diagnostic value.

The application of this test is made as follows: A solution is prepared by mixing one part of Koch's old tuberculin with one part of five-per-cent. phenol solution and two parts of physiological salt solution. The skin of the forearm now having been washed with ether, a lancet with a platino-iridium point is passed through an alcohol flame and used to scarify the skin, control scarifications being made at the same time in other parts of the arm. Two drops of the inoculation fluid above mentioned is applied to the scarified surface and allowed to remain in contact with it for a few minutes. A bandage or other dressing is not needed. The inoculated as well as the control spots are inspected daily for three days to determine the presence of the reaction above described. Eighty-eight per cent. of the children inoculated at a meeting of the Berlin Medical Society, May 8, 1907, presented positive reactions; twelve per cent. were negative. Among non-tuberculous children sixteen per cent. gave a positive reaction. Adults and older children apparently free from tuberculosis reacted readily, so that the diagnosis cannot be positively determined excepting in young children.

See also the article on *Ophthalmology-reaction*.

DIONIN is ethylmorphine hydrochloride, $C_{19}H_{23}NO_3 \cdot HCl + 2H_2O$. It is a white crystal with a slightly bitter taste, soluble in 7 parts of water, 2 of alcohol and 20 of syrup; insoluble in ether and chloroform. It is used as a substitute for morphine and is sedative, antispasmodic, and analgesic. Is precipitated from solutions by alkaloidal reagents.

Dionin is reported free from the constipating effects of the ordinary opium alkaloids, as well as nausea and lassitude. It is used internally in the cough of phthisis, bronchitis, asthma, insomnia, laryngitis, influenza, and whooping-cough, but appears to have no advantage over codeine. The claim that dionin is serviceable in the treatment of the morphine habit does not seem to be proven by use in these cases. This remedy is used somewhat as an application to iritis, various forms of painful conjunctivitis, etc.

The dose of dionin internally varies from 0.015 to 0.03 gm. ($\frac{1}{4}$ to $\frac{1}{2}$ grain); children, proportionately less according to age. In diseases of the eye, 1 to 2 drops of a five- to ten-per-cent. solution.

DISSOCIATION, DIFFUSION AND ACTION OF SALTS.—The advance of physical chemistry in the last few years has thrown a new light upon the behavior of salts in the tissues, and promises to form the basis of the explanation of their presence in all forms of living

matter, as well as of much of their therapeutic value. The chief phenomena bearing on biology and medicine are the dissociation of salts and their relation to diffusion and osmosis, and before the results of the application of physical-chemical methods to the biological sciences can be appreciated some knowledge of the recent advances in the theory of these phenomena is requisite.

Dissociation. Ions.—It was formerly held that common salt dissolved in water remained in the same form as that which is familiar in the dry state, the only difference being that crystals divided into molecules. It is now recognized, however, that not only are the molecules isolated from each other, but that a certain number of molecules undergo still further division. The products of this molecular division are known as *ions*, and in the case of common salt are Na ions and Cl ions. The amount of dissociation that occurs varies with the strength of the solution; the weaker the solution the greater the percentage of salt undergoing dissociation. In a one-per-cent. solution of sodium chloride only about one-fifth of the salt is present in the form of molecules, the rest having dissociated into the two ions. These ions are not to be confused with atoms, for although sodium and chloride ions are present, the solution of course possesses none of the properties of metallic sodium or of free chlorine. The ions differ from the atoms in carrying a charge of electricity, the charge of the sodium ion being positive, while that of the chloride ion is negative.

If a battery be connected with the solution the sodium ions hurry to the negative pole or cathode, while the chloride ions give up their charge at the positive or anode. The sodium ion is therefore known as the *cation*, the chloride as the *anion*. At the moment at which the charge of an ion is given up the ion changes to an atom, but it immediately forms fresh combinations with the water, in the present instance NaOH and HCl.

Other salts undergo a similar dissociation in solution in water: KBr forms K and Br ions; NaNO_3 , Na and NO_3 ions, K_2SO_4 divides into three ions, two potassium and one SO_4 ; ammonium oxalate forms two NH_4 ions and one oxalate anion, and so forth. The dissociation of acids and alkalis is of great importance, but resembles exactly that of the other salts, acids forming hydrogen cations and the rest of the molecule forming the anion, while alkalis divide into a hydroxyl anion and a metallic cation; HCl thus becomes hydrogen and chloride ions; NaOH, sodium and hydroxyl (HO) ions.

The ions in a solution are in constant motion, and the anions and cations of a substance in solution lose the connection which they possess in the solid state. Thus, when potassium bromide and sodium chloride are dissolved together in a sufficient amount of water, it is no longer correct to designate the result as a solution of potassium bromide and sodium chloride, for the potassium ions are in no closer connection with the bromide than with the chloride ions. The bodies present are really the potassium and sodium cations and the bromide and chloride anions. In the blood serum, for example, the phosphate ions present are not combined with the potassium nor the chloride with the sodium, but all four are independent, and it is incorrect to speak of the potassium phosphate of the blood serum. When a dilute solution of sodium hydrate is swallowed it is neutralized by the gastric juice, and the reaction is often stated as the formation of sodium chloride and water. In reality the hydrate solution contains sodium and hydroxyl ions, the gastric juice hydrogen and chloride ions, and the resultant fluid contains sodium and chloride ions. The change consists in the disappearance of the hydrogen and hydroxyl ions which have formed water, the chloride and sodium ions having been present to begin with and remaining unchanged.

Dissociation occurs in salts, including under this term acids and alkalis, but it is not developed equally in all salts. Those acids and bases which are generally considered to be the "stronger" dissociate more readily than the weaker combinations, and the monovalent salts more readily than the bivalent. The inorganic salts dissociate

more readily than the organic, and the same holds true for the bases. All of those bodies in solution serve as electrical conductors; in fact, the passage of electricity through watery solutions is only possible through the presence of ions, and the conductivity of solutions is thus a measure of the degree of dissociation. Those substances which are dissociable are therefore known as electrolytes. On the other hand, many organic substances are incapable of conducting electricity and are also incapable of dissociation. Thus alcohol contains an hydroxyl ($-\text{OH}$) in combination with ethyl (C_2H_5), as sodium hydrate contains an hydroxyl in combination with sodium. Alcohol is, however, incapable of forming ions, and therefore is a non-electrolyte in aqueous solution, while sodium hydrate dissociates readily into hydroxyl and sodium ions, and these are capable of conveying an electric current.

Sodium hydrate has a characteristic action in the tissues, causing corrosion. This might be due to either the sodium or the hydroxyl ion. As a matter of fact, however, the sodium ion is present in many solutions which are devoid of corrosive effects; for example, in solutions of sodium chloride. The conclusion, therefore, is that the hydroxyl ion is the corrosive in this case. Alcohol has no such corrosive action as sodium hydrate, and this corresponds with the fact that alcohol is not an electrolyte, *i.e.*, does not liberate the hydroxyl ion, although it contains hydroxyl. Many other similar examples might be cited, all going to show that in many instances the therapeutic effects of a body are due, not to the molecule administered, but to the ions into which it dissociates in the fluids of the body. In fact in administering an electrolyte, the physician gives not one but two or more substances, which may each effect changes in the organism. As a general rule in therapeutics one ion is so powerful that the other may be neglected; for example, in morphine sulphate the alkaloidal cation is so active that the sulphate ion may be ignored, and the sulphate has therefore the same effect as the hydrochlorate of morphine. When the two ions are more equal in pharmacological activity, however, each has to be taken into consideration; for example, magnesium sulphate dissociates into magnesium and sulphate ions, each of which has a retarding influence on absorption in the bowel, while magnesium chloride similarly forms magnesium and chloride ions, of which the latter is indifferent in the bowel. The sulphate of magnesium has thus a more powerful purgative action than the chloride, and is also more active than sodium sulphate, which forms the purgative sulphate and the indifferent sodium ions.

Another example of the importance of ions to the understanding of therapeutic action and to its successful practice is offered by the bromides. Potassium and sodium bromides have a depressant action on the central nervous system, and as this is absent in the case of the chlorides of these metals, it is obviously due to the bromide ion. Bromated camphor also contains bromine in chemical combination, and attempts have been made to substitute it for the bromides as a depressant. But bromated camphor does not dissociate and no bromide ions are formed, so that whatever properties it may possess, it cannot be compared with the bromides of potassium or sodium.

The action of salts depending on the ions, the intensity naturally varies with the rate of dissociation. This is well exemplified in the local effects of the heavy metals; such salts as the chlorides and nitrates, which dissociate readily, are much more active locally than the sulphates and organic salts which divide into ions less rapidly, provided, of course, that all are equally soluble and have no special characteristics, such as deliquescence. The newer views as to the dissociation of salts and the important rôle of the ions explain why such bodies as the ferrocyanides have the effects neither of iron nor of cyanides, for neither iron nor cyanide ions are formed from them in solution. Similarly the cacodylates differ from arsenous salts because they do not liberate the arsenous ion except after decomposition in the body. Now in the

case of potassium arsenite, the arsenite ion is the active constituent, and the cacodylates can possess this only when they are broken down in the tissues into arsenous salts. The slowly dissociating salts are thus often used to avoid the local action of the more irritant metals; for example, many of the recent compounds of iron have the advantage over the older salts of causing less local irritation, while they have practically the same effect on the blood formation. Similarly several new preparations of mercury have been introduced with the view of lessening the local action on the stomach and bowel, or of lessening the irritation induced by the hypodermic injection of mercury. These compounds, when soluble, are more slowly dissociated than corrosive sublimate, and, there being fewer mercury ions present at any one time, the local irritant action is accordingly reduced.

The disinfectant action of the heavy metals also depends largely upon ionization, for the destruction of the germs is due to a chemical reaction between the metal and the protoplasm of the microbes; and the larger the number of free ions the greater the tendency to union. The attempt has been made to obtain germicides devoid of the local irritant action by forming less readily dissociating salts than those in ordinary use. A large number of preparations have thus been introduced, partly compounds with organic acids, partly with proteid bodies. But as the irritant and the germicidal action of most metallic compounds depend on the same factor, namely, the free ions, it seems likely that the lesser degree of irritation induced by these is obtained only by the sacrifice of much of the disinfectant value.

The double salts are much less readily dissociated than the simple, and not infrequently appear to liberate somewhat complicated ions, as in the case of the ferrocyanides noted above. They are therefore largely devoid of the local action of the parent substances, and this may be taken advantage of in therapeutics occasionally.

When two salts which have one ion in common are dissolved together in water, the dissociation is considerably reduced. For example, if corrosive sublimate be dissolved along with sodium chloride, the former is less dissociated than if it were dissolved alone in the same amount of water. In accordance with this general rule, it is found that the addition of sodium chloride to a mercuric perchloride solution lessens both its irritant and its germicidal power, and in cases in which it is desirable to mitigate the former, and in which the latter is of no importance, as in the treatment of syphilis by the hypodermic method, this mixture may be used instead of the pure mercuric salt.

The complete treatment of the dissociation of salts would involve a large part of pharmacology and therapeutics, in which the importance of the phenomenon is daily becoming more evident. The inorganic *materia medica* is more dependent on the principle than the organic, as the dissociation is much more complete in the former. It is possible to exaggerate the importance of the new law, however, for many of the facts and principles of therapeutics remain unaltered by its introduction. For example, it is undoubtedly more in accord with modern theory to attribute the effects in epilepsy to the bromide ion than to the bromides, as was formerly done, but this is after all a matter of nomenclature, and it is perhaps necessary at the present time to remember that there was a science and practice of therapeutics before the ion theory was broached. On the other hand, there can be no question that it has thrown much light on many questions, and removed many misconceptions. In the case of the bromides, for example, it is scarcely possible to maintain at the present time that the bromide of ammonium is superior to that of sodium, except possibly in regard to the local action on the alimentary tract, for in each case the active constituent is the bromide ion, and this is equally readily furnished by either salt.

In physiology and biology generally the theory of ions is of great importance, as is at once apparent from the fact that the fluids and tissues of the body can only conduct the electric current through the presence of ions.

Every electric stimulus causes a change in their distribution, and every electrical discharge (and electrical changes accompany every movement and every other form of activity) is intimately connected with the presence of free ions, and in fact is possible only in their presence. The whole of electro-physiology, and naturally of electro-therapeutics, has thus to be based on the ionic theory, and the fact that every life process so far investigated has proved to be accompanied by electric changes indicates that the presence of free ions is necessary to life itself. This of course agrees with the fact that inorganic salts are present in every living tissue.

Not only do living tissues require the presence of free ions, but even dead colloid material is altered very remarkably by them. And certain facts have recently been brought out in regard to the dependence of the proteids on certain ions which promise to have a far-reaching influence on biology and hence on medical science. It has long been known that many proteids, notably the globulins, are precipitated from solution when such salts as the sulphates of magnesium or ammonium are added to them. But Hardy has recently shown that the precipitation and solution of colloids, such as the proteids, depend largely on the valency of the ions present in the solution. Thus bivalent cations precipitate some colloids in comparatively small quantities, and trivalent cations are still more efficacious, while monovalent cations tend to keep them in solution or have a very much smaller precipitating action. The bivalent and still more the trivalent cations thus tend to oppose the monovalent cations in regard to colloid solubility; and as ions are necessary to the life phenomena, the monovalent must be counterbalanced by the bivalent in the tissues, for either of these alone would tend to change the colloids from the normal condition to one of excessive or deficient fluidity.

A good deal of interest has been aroused in regard to the antagonistic action of ions in living tissues, which is found to present some similarity to that described by Hardy in dead colloid matter. The organ examined with most care in this relation is the frog's heart, a very sensitive reagent to changes in its environment. It has long been known that the excised frog's heart will beat for a long time when supplied with oxygenated blood or serum, and also in fluids containing no organic matter, but merely the inorganic salts of serum. On the other hand, solutions of non-electrolytes, such as sugar, fail to maintain the contractions. The presence of ions in the perfusing fluid is therefore necessary to maintain the heart in activity. But all ions are not equally efficient, for a certain amount of sodium chloride is found to maintain the contractions longer than any other single salt. The contractions very soon become weaker in sodium chloride solution, however, and finally the heart is arrested. But this arrest may be prevented if the solution contain in addition to sodium chloride a trace of a calcium salt; on the other hand, a heart which has ceased to beat in sodium chloride solution may be induced to resume its pulsations if calcium be added to the perfusing solution. This phenomenon was first noted by Ringer,* and has been confirmed by all subsequent observers; but views differ as to the interpretation to be given it. Howell has upheld the theory that sodium and calcium are both necessary to the heart, and that when sodium chloride solution is perfused alone, the calcium in the heart muscle diffuses out and is washed away and the heart ceases from its losing one of the necessary constituents, calcium. In support of this view he has shown that when the lime ions are removed by other means, *e.g.*, by precipitating them with oxalates, the heart ceases to beat.

Loeb, on the other hand, holds that the heart can only beat in solutions of electrolytes, and that the least poisonous of these is formed by sodium and chloride ions. Even these are not altogether harmless, however, and after a time the heart ceases from poisoning with the so-

* Ringer's solution, which has been widely used in physiology as that most suitable for conserving the life of tissues, contains sodium, potassium, calcium, chloride, phosphate and carbonate ions and is made up of 100 c.c. of 0.75-per-cent. NaCl, 5 c.c. of 0.25-per-cent. CaCl₂, 2.5 c.c. of 0.5-per-cent. NaHCO₃ and 0.75 c.c. one-per-cent. KCl.

dium ion. Calcium ions are antagonistic to sodium, and the addition of lime salts therefore reinstates the contractions. To put it shortly, the heart ceases in sodium chloride solution because, according to one view, a necessary constituent, calcium, is all washed out, according to the other, because the sodium is poisonous and has to be antagonized by the lime. Loeb's view appears, at first sight, the less plausible of the two, because it has been held that sodium chloride is a perfectly indifferent substance to animal tissues. It must, however, be remembered that here there is always sufficient calcium present to neutralize any poisonous action of the sodium, and this argument has therefore little weight. On the other hand, he has brought forward some very telling facts in its favor in his investigations of other organs than the heart. Without going into all of these, it may be mentioned that he found striated muscle undergo irregular twitching contractions in sodium chloride solution, but these were arrested by calcium and other bivalent salts, so that the phenomenon is not confined to the heart muscle. Loeb found a small fish, fundulus, which lives in sea water or in distilled water indifferently, but dies in a solution of sodium chloride of the same density as sea water. This can only be interpreted as indicating that there is something present in sea water which prevents the poisonous action of sodium chloride. On investigating the subject further he found that in a solution of sodium chloride, to which traces of calcium salts were added, the fundulus and its eggs lived as well as in sea water. The conclusion is inevitable that the lime normally present in sea water antagonizes the poisonous action of sodium chloride in this case. The parallel between the behavior of this animal and that of the frog's heart and other organs is so close as to form an important support for Loeb's theory of the interaction of the ions. It may be added that numerous examples of a similar antagonism are already known in more complicated ions than sodium and calcium. Thus the antagonism of atropine and pilocarpine, of curarine and physostigmine in striated muscles, and of the central nervous depressants and strychnine is similar, although these differ in not being essential to the function of the organs on which they act.

It is to be noted that in the case of fundulus, the action of sodium chloride is antagonized by a comparatively minute amount of calcium, and also by corresponding small quantities of other bivalent and trivalent ions, such as those of barium, strontium, lead, zinc, chromium, and alum. Similarly calcium removes or lessens the poisonous effects of potassium salts on the heart, and the potassium ion is also necessary to the normal contraction, so that the antagonism is believed by some observers to be related to the valency of the metallic ion. The fact that electrolytes are necessary to the heart and other organs suggested to Loeb and Mathews the view that the antagonism is due, at any rate in part, to the electric charge carried by the ions, but this is very far from being proved or from being generally accepted. For it has been found that striated muscle, which undergoes abnormal contractions in solutions of several monovalent salts, fails to do so in all; and while the contractions are arrested by some bivalent metals, others have not this effect. The conclusion seems justified that the antagonistic effects are not immediately associated with the valency or the electric charge, but are the results of some unknown special relation between the ions and the protoplasm, these relations differing in different organs and for different metals. In other words, the calcium-sodium antagonism appears to be of the same nature as the atropine-pilocarpine one, and is equally inexplicable in the present stage of knowledge.

While each of the cations alone is poisonous and has to be antagonized by some other cation, ions are necessary to the life processes. Protoplasm can exist then only in the presence of a number of different salts, of which the chief liberate sodium, chloride, calcium, and potassium ions. The poisonous effects of sodium are counteracted by very small quantities of calcium, the ratio obtaining between those in the best media being about 1,000 to 1.

An electric current can be conducted through a watery solution only by means of the ions at liberty in it. The extent of dissociation in the fluid may therefore be estimated by the conductivity of the solution or inversely by the resistance met by the current. As long as there is only one salt in solution the calculation is simple and the results are unequivocal. And however many bodies are in solution, the amount of dissociation may be estimated, although if large amounts of undissociable matter (non-electrolytes) be present the results are too low. But such estimations give no clew to the nature or relative amounts of the salts in solution. Some efforts have been made to apply this method to the examination of the urine and the blood in the hope that light might be thrown on the condition of the kidney by its means. As a matter of fact, however, the urine is much too complex in its composition to permit of results of much value being obtained. The chief electrolytes here are the chlorides, and a small variation in their percentage may induce a large deviation in the resistance, while if the chlorides vary in one direction and the other salts in the opposite, the resistance may remain almost unchanged in spite of great alterations in the composition of the urine. The chief non-electrolyte is the urea, and its presence in large amount may increase the resistance without any marked change in the amount of salts or their dissociation having occurred. The method cannot therefore be regarded as replacing the chemical analysis of the urine, for its results are of a totally different kind. And it has not been shown by observation that the results obtained by measuring the electrical resistance can be utilized for diagnosis or to indicate the value of therapeutic measures.

Diffusion and Osmotic Pressure.—When distilled water is carefully poured upon a solution of sugar so that the two liquids do not immediately mix, the sugar molecules soon begin to penetrate into the pure water, and after a sufficient lapse of time the contents of the vessel become homogeneous, the percentage of sugar in what was distilled water being the same as in the part corresponding to the original solution. The explanation is that the molecules are in constant movement and, diffusing in all directions, some of them penetrate into the pure water, and this process goes on until the latter contains as many particles as the original. The movement still continues, but now as many molecules diffuse back into the lower layer as into the upper so that equilibrium is maintained. The process is the same as that seen when a crystal of sugar is dissolved, for here also the constituent molecules leave each other and wander throughout the fluid.

When a membrane is stretched between the two fluids, the result varies with its character. If the membrane offers no resistance to the passage of water and sugar, the same phenomenon is observed as if they were not separated by a membrane; the fluid on each side becomes homogeneous, although this generally takes more time, owing to the fact that currents are less liable to aid the process. If the membrane be permeable to neither sugar nor water, of course the fluids remain completely isolated and unchanged. On the other hand, some membranes, known as semipermeable membranes, permit the passage of water and not of sugar. For the sake of clearness, suppose that a solution of sugar be placed in the upper vessel of a diffusion apparatus with a semipermeable membrane, and distilled water in the lower. In this case the molecules of water in the lower vessel can penetrate into the upper, while on the other hand those in the upper cannot escape into the lower. The reason for this is simple; for if water escaped from the sugar solution without an equivalent amount of the sugar, the solution would be more concentrated. Now in order to concentrate the sugar solution, work has to be done; for example, it may be concentrated by heating it. But in the diffusion apparatus there is no source of energy available for concentration, and the result is that the water cannot escape from the upper vessel. On the other hand, the membrane being permeable for water, the molecules in the lower vessel find no difficulty in entering the upper. The result is that the sugar solution becomes more dilute,

while the water in the lower vessel diminishes in volume until it may disappear altogether. If sufficient pressure be applied to the sugar solution, the water will cease to enter it from the lower, and the amount of pressure which suffices to arrest the movement of the water is known as the *osmotic pressure* or *osmotic tension* of the sugar solution. The phenomenon is known as *osmosis*, but it must be recognized that osmosis is merely a diffusion under special circumstances, for the whole is due to the movement of molecules, all of which are free in ordinary diffusion, while some of them (*e.g.*, sugar in the above example) are restricted in their movements in osmosis.

The osmotic pressure is found to vary directly with the number of molecules in the solution, a concentrated solution causing a more rapid flow and a higher pressure than a more dilute one. Thus a one-per-cent. solution of cane sugar exercises a pressure of 535 mm. of mercury, a two-per-cent. of 1,070 mm., and so on. The pressure exercised by even dilute solutions is very considerable, as is seen on transforming these figures into atmospheres, for a two-per-cent. sugar solution is then found to give a pressure of nearly one and a half atmospheres. This is even more remarkable when a smaller molecule than sugar is chosen. Thus a one-per-cent. solution of potassium nitrate exercises a pressure of over three atmospheres. As the pressure depends upon the concentration of the solution, it decreases and the movement becomes slower as the process goes on, for the water diffusing into the sugar solution dilutes it.

As osmosis is merely a special form of diffusion, it follows that only diffusible and dissolved substances can exercise osmotic pressure. The colloids, such as proteids, are therefore generally believed not to have any influence on the movement of fluids because they are not in true solution, but rather in a state of suspension. Others hold that though in solution, they exercise no appreciable tension because the molecule is so large. As each molecule in solution has the same osmotic effect, it stands to reason that a one-per-cent. solution of sugar must induce an immensely greater pressure than a one-per-cent. solution of albumin, because the number of molecules dissolved in the former is so much greater. The proteids always contain a certain amount of soluble salts, and these are sufficient to cause some osmotic tension; so that it is not yet decided which explanation is correct, but in any case the osmotic pressure of the proteids is so small as to be negligible.

Very often membranes are met which offer a certain amount of resistance to the passage of dissolved diffusible bodies while allowing water to pass freely. If such a membrane separated a sugar solution and water, the latter would at first pass through into the solution rapidly under considerable osmotic pressure. But some sugar also passes downward, and there is thus formed a strong solution of sugar above rapidly being diluted and a weak solution of sugar below rapidly becoming stronger from the continued permeation of sugar into it and the escape of water upward. Finally equilibrium is reached by the solutions on each side of the membrane attaining the same concentration.

The same principles hold when solutions are present on each side of the membrane, the direction of flow being always toward that side on which the larger number of molecules are present, provided the membrane is semi-permeable. The osmotic pressure is determined by the difference of the osmotic pressures of the two solutions toward distilled water. If the same body is in solution on the two sides of a permeable membrane, the water tends to pass toward the stronger solution, while the solid passes in the opposite direction until equilibrium is reached. When two different bodies in solution, *e.g.*, sugar and urea, are separated by a membrane which is permeable by each of them, they diffuse freely through it and the two solutions soon become identical, each containing the same percentage of urea and sugar. If the urea can penetrate the membrane while the sugar fails to do so, the osmotic pressure is that of the sugar solution and the urea solution will pass toward the sugar as long

as the latter can exert appreciable pressure. In other words, no osmotic pressure is exerted by a fluid toward a membrane which it can pass through.

When neither sugar nor urea can pass through the membrane, the water passes from the solution containing the smaller number of molecules toward that containing the larger number until equilibrium is established by each solution containing the same number of molecules per cent. of water. The weaker solution is often known as the *hypotonic* or *hypoosmotic*, the stronger as the *hypertonic* or *hyperosmotic*, while two solutions possessing the same osmotic pressure are known as *isotonic* solutions.

In biology the problems in diffusion are much more complex than the examples given above, but they all depend on these general rules. In the first place the solutions are much more complicated, containing a number of different substances in solution; in the second, the membranes are neither perfectly permeable nor semipermeable. They permit the passage of some of the constituents of the fluids, but as a general rule few of these pass quite freely, and the amount of resistance varies with each kind of molecule. Further it must be recognized that a dissociated salt exercises not the osmotic tension of a molecule, but that of its ions. In a dilute solution of sodium chloride, for example, the osmotic pressure is not measured by the number of molecules, for each ion exercises the same osmotic effect as a molecule of sugar, or as an undissociated molecule of salt.

Each cell in the body may be conceived as the inner vessel of a diffusion apparatus, separated from the surrounding fluids by a membrane, for though this membrane has no anatomical existence, the colloid nature of protoplasm has the same final effect as if the cell were surrounded by a membrane. All cells are permeable by water, but each kind of cell appears to differ in the facility with which it permits the permeation of salts and the other bodies dissolved in the body fluids. Some, for example, allow the passage of ammonium readily, while others refuse it entrance. Others take up sodium sulphate as readily as sodium chloride, while others accept the latter and reject the former. Now if the intercellular fluid contains any substance which is not capable of penetrating the cells, it must exert osmotic pressure on the cell; and unless this pressure is counterbalanced by other bodies in the interior of the cell which similarly cannot escape from it, the fluid of the cell will be drawn out and shrinkage will result. Every cell in the body then must be conceived as existing in a condition of equilibrium, the osmotic tension of the salts, etc., in its interior being pitted against that of the surrounding fluid, and the smallest change in either of these leading to an inflow or outflow of water from the cell. Now such changes are continually in progress, for as the proteids and carbohydrates of the cells are broken down into simpler bodies, soluble in water, each molecule so formed acquires osmotic properties, and either diffuses freely into the surrounding fluid, or causes an inflow of water into the cell. In either case the equilibrium is disturbed until the new product is removed by the excretory functions. The importance of diffusion and osmosis in the functions of the body cannot therefore be overestimated; in fact, it may be said that while the more obvious movements of the fluids of the body are determined by the circulatory mechanism, the finer but no less important exchange between the cells and the intercellular fluid is in large part directed by the laws of diffusion. And while a knowledge of the arterial supply of an organ is recognized to be necessary for an understanding of its physiology and pathology, it is probably no less desirable to ascertain the permeability of its cells for the constituents of the surrounding fluids. The osmotic pressure varying with the nature of the membrane or cell, and also with the salt in solution, the only way to determine the results of exposing the cell to a solution of the salt is the experimental, and a considerable amount of work has been done in this direction, so that the permeability of some cells is known for a large number of salts and other bodies. In this method of procedure the cells under examination, *e.g.*,

the red blood cells, are exposed to solutions of different strengths, and the concentration which induces neither shrinking nor swelling of the cell is ascertained. This concentration is that balanced by the intracellular fluid, and the solution is said to be isotonic for that cell. The salt in solution must obviously fail to penetrate the cell, or do so only extremely slowly, for if it permeates freely the water in which it is dissolved will also pass into the cell and expand it. In such an isotonic solution the number of molecules percent is exactly equal to that in the interior of the cell, and a solution containing the same number of molecules and ions of any other non-permeating salt will also be isotonic and cause no change in the size of the cell. For example, if a 0.75-per-cent. solution of sodium chloride has been found isotonic for the blood cells, an equivalent solution of sodium sulphate or of ammonium chloride will also preserve the size of the cells unchanged, provided these salts are equally incapable of permeating the cell. If one of these, *e.g.*, that of ammonium chloride causes swelling of the cell and the escape of hæmoglobin, then this salt must permeate more freely than sodium chloride.

In the case of non-dissociating bodies, such as alcohol, sugar, or urea, equimolecular isotonic solutions can be made by calculating the atomic weights. In the case of the salts this method fails, for the dissociation varies for different salts and for different dilutions, and each ion exercises the osmotic pressure of a molecule. Other methods have therefore been adopted, and of these the estimation of the depression of the freezing point has come into general use in the last few years. This method, it must be emphasized, does not indicate the osmotic pressure for all membranes, nor the permeating qualities of the substance, but only the total number of molecules and ions in the solution. It depends upon the fact that solutions containing the same total number of ions and molecules per cent. freeze at the same temperature, which is lower than that at which distilled water freezes to ice. If two solutions lower the freezing point an equal extent below 0°C ., therefore, they contain the same number of ions and molecules, and are isotonic toward a semi-permeable membrane. The estimations are made by means of thermometers reading to $\frac{1}{100}^{\circ}\text{C}$., and allowing of approximations to $\frac{1}{1000}^{\circ}\text{C}$., and with some care and practice in the method very exact determinations may be made. A very extensive use of this freezing method has been made in experimental work, and some results have also been obtained in clinical medicine, but the details of the method can only be given in works dealing specially with this subject. The depression of the freezing point of any solution below that of pure water is generally expressed by the symbol Δ . If the salt is not capable of penetrating a cell, its osmotic pressure varies with the Δ of the solution, *i.e.*, with the concentration of molecules and ions, and if two solutions of non-permeating salts have the same Δ , their influence on the movement of the fluid of the cell will be equal. On the other hand, if the salt permeates without difficulty, the Δ is of no significance in regard to the effects of the solution on the cells.

The relations of the salts to the tissues has been worked out in most detail in the case of the red blood cells. It is found that in a 0.75-per-cent. solution of sodium chloride, the cells maintain their form and size unchanged, *i.e.*, the salt fails to penetrate the cells and exercises the same osmotic pressure as the diffusible contents of the cells, or is isotonic with the fluid in the interior of the cell. If the cells be exposed to pure water, they swell up and discharge their hæmoglobin, and the same occurs in weak (hypotonic) solutions of sodium chloride. The salt here being in lower concentration than the contents of the corpuscles, a current of water sets inward toward the stronger solution. In solutions of greater concentration than 0.75 per cent. (hypertonic solutions) the cells shrink from the loss of water, which flows outward toward the stronger solution. Similar phenomena are seen when other salts of the fixed alkalies are employed, so that these salts appear to be unable to penetrate the corpuscles except to a very slight extent.

In solutions of ammonium chloride, on the other hand, the cells swell up and lose their hæmoglobin, whether the solution be isotonic with 0.75-per-cent. NaCl, or much stronger. The conclusion is that the ammonium chloride can penetrate the cells and thus exercises no osmotic resistance to the entrance of water, so that the effect of ammonium chloride solution is practically identical with that of pure water. Many other ammonium salts resemble the chloride in penetrating the red blood corpuscles; but others, such as the sulphate and phosphate, fail to enter the cell entirely, or penetrate with great difficulty. The sulphate and phosphate ions, therefore, like the sodium and potassium ions, are non-permeating, and exercise osmotic pressure on the cell wall. Unless both ions of a salt can enter the cell, neither does so. Many non-electrolytes, such as urea and compound ammonias, appear to enter the blood cells freely.

The absorption of salt solutions in the intestine also presents an interesting example of the importance of diffusion in vital processes. A solution of sodium chloride isotonic with the blood is absorbed readily, whence it is inferred that sodium chloride can penetrate the mucous membrane. A hypotonic solution is similarly taken up easily, and still more readily pure water. A hypertonic solution, on the other hand, disappears from the bowel more slowly, and very often the fluid first increases in the lumen until it has become almost isotonic with the blood, and only then disappears into the tissues. The sodium chloride does not, therefore, permeate the bowel wall without resistance, otherwise a hypertonic solution would be taken up as quickly as distilled water. On the contrary, a hypertonic solution first exercises osmotic pressure on the cells and causes them to lose water. At the same time some of the chloride has disappeared into the cells, and the solution remaining is diluted with the water exuding, until it is so weak that the osmotic resistance is overcome by the absorbing forces and the whole is absorbed into the blood.

When the sulphate of sodium passes into the bowel in solution, this feature is still more marked. An isotonic solution has little tendency to be absorbed, and on the other hand is not increased in volume, the solution in the bowel counterbalancing the osmotic pressure of the cell contents. A hypotonic solution decreases slowly because its osmotic pressure is less than that of the cell contents, and water therefore tends to pass from the weaker fluid in the lumen to the stronger in the blood; but the fluid escapes from the bowel much more slowly than in the case of an hypotonic solution of sodium chloride. If hypertonic solutions be used, the bulk is at first much increased owing to fluid from the blood escaping into the stronger solution. Finally the sulphate solution becomes isotonic with the blood and is very slowly absorbed if the weight of the fluid in the bowel does not set up reflex peristalsis and cause evacuation. This slow absorption from the bowel is still more marked in the case of magnesium sulphate, in which both ions appear to be taken up with reluctance by the mucous membrane. As these salts fail to leave the bowel and retain the water in which they are dissolved, they render the contents more fluid than usual, and the unusual weight and distention cause peristaltic movements and evacuation. The purgative action of the saline cathartics arises from the difficulty with which they enter the epithelial cells. It is to be remarked that here, as in the case of the red blood cells, the sulphates diffuse with greater difficulty than the chlorides; on the other hand, the chlorides of the fixed alkalies are taken up freely by the bowel wall, while they fail to permeate into the corpuscles, and the oxalate of ammonium, which penetrates the blood cells, is rejected by the epithelium.

The presence of the salt solution in the stomach and intestine inducing such movements of fluid into the bowel and back into the blood, naturally causes considerable disturbance in the distribution of the fluids of the body. When a strong sulphate solution is diluted by fluid poured into the intestine, for example, this fluid comes from the blood and indirectly from the fluids of the tissues. A similar exchange without doubt follows the ab-

sorption of salt solutions into the blood, but this is difficult to follow experimentally. When salt solutions are injected into the blood-vessels, however, it is found that there is a marked disturbance of the equilibrium of the tissues. If the solution is hypertonic, there is a flow from the lymph spaces toward the blood which continues until the plasma recovers its normal density. The current then is found flowing in the opposite direction from the blood-vessels into the tissues. The lymph measured in the thoracic duct is found to be lessened at first owing to the inflow into the vessels, but later more lymph passes along the duct than usual, owing to the current of fluid passing toward the tissues from the blood.

The injection of salts into the blood-vessels or their absorption from the bowel leads to considerable diuresis. The explanation of this diuresis is still a matter of discussion, but there can be no question that the diffusion and osmotic properties of the salts play an important rôle in this result. The accumulation of fluid in the blood at the expense of the tissues naturally leads to an unusual bulk of the contents of the blood-vessels, and this in turn to an increased pressure in the capillaries. This engorgement of the vessels cannot be relieved by an outflow into the tissues, for this is prevented by the current of lymph pouring into the vessels. Only one way of escape remains, that through the kidneys, and the inflow of lymph is therefore accompanied and followed by diuresis, which is thus in large part explained by the physical forces, although there is doubtless much still obscure in the process. Different salts vary in their diuretic properties, and this might at first seem to indicate that the diffusion was of secondary importance. As a matter of fact, however, many of these differences can be explained by varying rates of diffusion. For example, the sulphates are as a general rule inferior diuretics when given per os, because they fail to reach the blood for the most part from their cathartic action. On the other hand, sulphate of sodium, injected intravenously, causes much greater diuresis than an equimolecular solution of sodium chloride, even if it causes the same inflow into the vessels and the same degree of hydræmia. This has been explained, however, by the renal tubules failing to absorb the sulphate, while taking up the chloride readily. If this is the case, as appears very probable, the sulphate failing to penetrate the renal tubules and thus return to the blood, must hold a certain amount of water in the tubules which would otherwise return to the blood. The chloride, on the other hand, returns readily through the epithelium lining the tubules, and thus retains less water in the tubules and causes less diuresis. In this view the epithelium of the tubules resembles that of the intestine in repelling sulphates and phosphates and admitting chlorides readily, but differs from it in showing little avidity for urea and sugar.

The urine is generally a much more concentrated fluid than the blood; that is, it contains a larger number of molecules and ions. The kidney must thus do a considerable amount of work in concentrating such a fluid from the more dilute blood plasma, and by estimating the Δ of the blood, which is remarkably constant (about -0.56°C.), and comparing it with that of the urine, the actual work done may be estimated exactly. Dreser calculated the work done by the kidney in forming 200 c.c. of average urine at the large sum of 37 metre kilograms, or over 270 foot-pounds, but this may be greatly exceeded in cases of very concentrated urine. Attempts have been made to use this method of estimating the work of the kidney in clinical medicine, and the subject has been treated of at great length in recent years under the title of cryoscopy. As yet no results of importance bearing on diagnosis or prognosis in renal affections have been arrived at.

When very concentrated solutions of salts or other diffusible bodies are brought in contact with living cells, some fluid escapes from these into the solutions, and this often deranges the activity of the cell. This may be observed in the stomach when strong solutions of such harmless bodies as common salt or sugar are swallowed,

the disturbance of the equilibrium manifesting itself in irritation, nausea, and vomiting. In the same way a strong solution applied to wounds or mucous membranes causes irritation and pain from the withdrawal of fluid and precipitation of proteids. The same desiccation of the tissues may arise to a less degree from the presence of excess of salt or sugar in the blood. The organs which suffer chiefly are the brain and spinal cord, as is manifested in tremors and convulsions, and later by paralysis and asphyxia, when strong solutions of salts, sugar, urea, or other diffusible substances are injected intravenously in animals. *Arthur R. Cushman.*

DUCTUS ARTERIOSUS.—*Synonyms:*—Ductus arteriosus Botalli, Ductus Botalli, Arterial canal, Arterial duct.

This atypical blood-vessel represents the remains of part of the fourth left arterial arch of the early embryo, which functionates until birth to carry part of the blood from the pulmonary artery to the aorta, but immediately after birth it becomes occluded, and eventually it becomes completely obliterated. At the time of birth it is as large as or even larger than the main divisions of the pulmonary artery, being from 5 to 7 mm. in diameter, and from 4 to 20 mm. long, generally 9 to 12 mm. (Gérard). It arises from the pulmonary artery at the bifurcation,

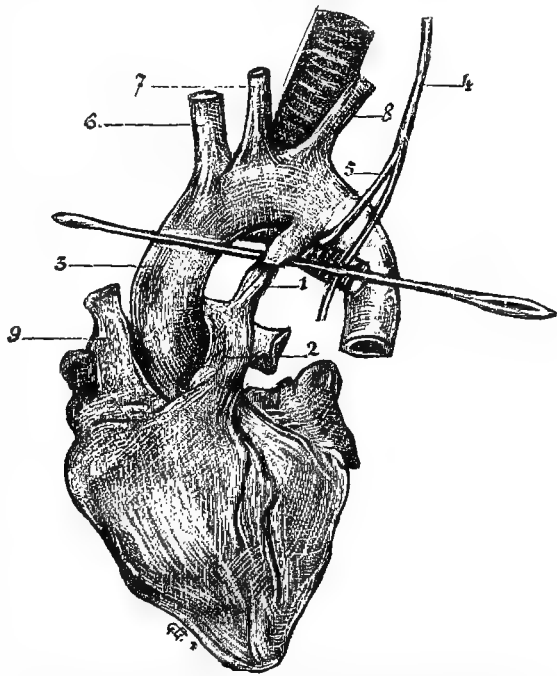


FIG. 5136.—The Ductus Arteriosus, after Dissection of the vessels at the Base. (Gérard.) 1, Ductus arteriosus; 2, pulmonary artery; 3, aorta; 4, pneumogastric nerve; 5, recurrent nerve; 6, innominate artery; 7, left common carotid; 8, left subclavian artery; 9, superior vena cava.

or a little to the left of this point, and passes first horizontally, then slightly downward, nearly paralleling the arch of the aorta, which it enters opposite to and a trifle below the origin of the left subclavian artery, and a short distance above the first intercostals. Its most important relations are to the pericardium, immediately outside of which it begins, passing in front of the left bronchus, and being encircled at its entrance to the aorta by the left recurrent laryngeal nerve. Histologically it presents the usual features of arteries of this size, but it is unusually poor in elastic fibres, a large proportion of which run longitudinally in bundles, and the muscular coat is not well developed. It is not strong, being readily torn, and will withstand but little more than the normal fetal blood pressure without abnormal dilatation and tearing of its coats (Roeder).

As soon as the new-born infant begins to breathe, the duct becomes at once occluded, and later the lumen is entirely obliterated. The mechanism by which the first occlusion is accomplished is not yet fully determined. Among the most reasonable of the many hypotheses advanced are: (1) That fibrous bands which are connected with the diaphragm pass around the duct, and occlude it when the dome of the diaphragm is first drawn down in respiration (Forbes). (2) That the changes in relative position of the great vessels and the thoracic viscera, that results from the filling of the lungs, draw out the duct until its walls are in apposition, and thus occlude its lumen (Schanz, Gérard, and others). (3) That on account of the acute angle at which the duct enters the aorta a valve-like fold is formed which pre-

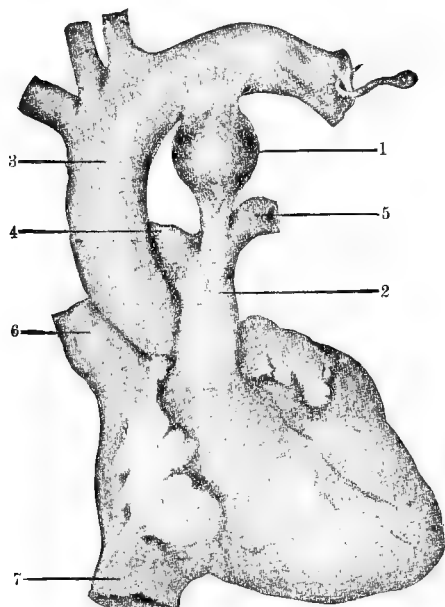


FIG. 5137.—Aneurism of the Ductus Arteriosus. (Gérard.) 1. Aneurismal enlargement; 2. pulmonary artery; 3. aorta; 4, 5, right and left branches of the pulmonary artery; 6, vena cava superior; 7, vena cava inferior.

vents blood from entering from the aortic end, although leaving the passage free for the entrance of blood from the pulmonary system when, as in the foetus, the pressure is higher there than in the aorta. (Zuntz, Strassmann). The last theory seems to have received the best support. When the circulation of blood through the duct stops, proliferative changes in the fibrous elements of the duct, especially in the intima, lead to its obliteration and conversion into a fibrous cord, the *ligamentum arteriosum*, which persists in the adult. The channel does not become entirely impermeable until some time after birth, usually between the 30th and 40th days, although often much earlier; a minute passage may remain for years.

PATHOLOGY.—Congenital Anomalies.—Almost every abnormal developmental condition about the heart and great vessels may be accompanied by abnormalities in the ductus arteriosus, such as: Absence, abnormal shortness, duplication, abnormal origin or insertion, premature occlusion. In most cases these are merely an accompaniment of the more important deformity of the heart and vessels.

Persistent Patency.—Whenever there exist congenital anomalies in the heart and great vessels that are not incompatible with life, the duct may fail to close, because the normal changes in the relation of aortic and pulmonary blood pressure do not take place at the time of birth. In congenital pulmonary stenosis the pulmonary circulation is largely carried on by blood reaching the pulmonary

arteries through the duct; and in congenital aortic stenosis the pulmonary artery supplies blood for the general circulation through the duct, as in the foetus. Primary persistence of the duct without other abnormalities is an extremely rare condition, constituting but about four per cent. of the recorded cases of congenital diseases of the heart and vessels. In 1898 Vierordt could collect but 26 cases, and in 1907 I was able to add 15 to this list: of the 33 cases in which the sex was recorded there were 12 males and 21 females. The chief predisposing cause seems to be respiratory difficulties in early life which keep the pulmonary blood pressure high and prevent occlusion; premature birth, abnormal insertion of the duct, abnormally large calibre, and simple failure of the occluding apparatus may also be responsible in some cases. Congenital syphilis does not seem to have been observed as a cause, but paternal alcoholism is frequently recorded. It is also possible for a duct that has been properly occluded, but only imperfectly obliterated, to reopen again under the influence of the aortic pressure, possibly after several years. Four anatomical forms of patent duct were recognized by Gerhardt: (1) Abnormal shortness; simply an opening between the aorta and the pulmonary artery; (2) funnel-shaped, with the wide end toward the aorta; (3) cylindrical form; (4) aneurismal dilatation. Frequently the pulmonary opening, which is usually smaller than the aortic, is surrounded by fibrous folds or a ring. The condition has been observed at all ages up to 66 years, and unless the size of the opening is large the results are not necessarily serious, although a greater or lesser degree of incapacity usually results; however, evidences of severe cardiac incompetence have been present in many of the cases, and death may result from this cause. Spontaneous healing by occlusion of the pulmonary opening may take place. The chief diagnostic features are: A systolic thrill, palpable best in the left second and third intercostal spaces, following the apex beat and continuing into the diastole; a murmur of corresponding duration and location, transmitted into the carotids and also heard posteriorly in the left superior interscapular region; a band of dulness along the left side of the sternum as high as the second rib, due to dilatation of the pulmonary artery, and the presence of a corresponding shadow in radiographic pictures. Cyanosis is less prominent than in most other congenital cardiac abnormalities, and often it is absent. Pressure has been produced on the left recurrent nerve.

Thrombosis of the duct is not an essential part of its obliteration, as once thought, but is a relatively uncommon occurrence. It is occasionally present in infants dying from septic conditions, and adults with a patent ductus arteriosus may show vegetations in the duct secondary to extension from an acute endocarditis.

Aneurism of the duct has been described in about a dozen cases, usually in infants a few days old. These aneurisms are occluded by thrombi, and represent what is probably not an extremely uncommon condition. Two cases of rupture of the duct in the new-born have been described by Roeder, and attributed to high pressure during labor, or from other causes.

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DWARFISM.—Nanosomia or microsomia is a condition in which the stature and weight fail to reach the normal minimum for individuals of the same species. The word *nanosomia* is derived from *ναῖος*, a dwarf, and *σῶμα*, a body. The Latin equivalent is *nanus* or *pumilio*, the Anglo-Saxon *dwæorg* or *dwærg*, and the German *Zwerg*.

Belief in the existence of dwarfs has prevailed from remote times. Homer, Herodotus, and Aristotle speak of a pigmy race that was to be found near the sources of the Nile. In India, too, there was a current belief in dwarfs descended from Hoonuman, the monkey-god. Many of the statements in regard to dwarfs are, however, so wildly improbable that they were, no doubt, based on mere "sailors' yarns," and are entitled to about the same amount of credence as the famous "Travels" of Sir John Mandeville. That they contain a modicum of truth, nevertheless, is proved by the discovery of diminutive peoples by modern explorers, such as Paul Du Chaillu, Schweinfurth, Battel, and Kolle. Dr. Schweinfurth, for instance, has found in the country to the south of the Nyam-Nyam a race called the Akkas, varying in height from four feet to nearly five, who are probably the same as those referred to by Herodotus. Any exhaustive discussion of the subject of dwarfism from an ethnological point of view would be out of place in a work of this nature, which is more properly concerned with the biological and pathological problems involved, but yet, apart from the interest that always invests the curious, it may not be entirely stale, flat, and unprofitable to possess ourselves of the main facts.

From the golden days of imperial Rome it was the fashionable thing to keep dwarfs. The most famous of these were Conopas and Andromeda, belonging to Julia, the niece of Augustus, each of whom measured only two feet four inches. Many of these dwarfs were, no doubt, the natural article, but the number of these was insufficient to supply the demands of cruel display and luxury; consequently they had to be produced by artificial means. One favorite method was the simple one of depriving children of suitable food. They became rickety, and while many died, those who survived were highly prized. Another plan, in some vogue, was to rub the back with the fat of bats, moles, or dormice. Somewhat similar was the practice of washing the backs and feet of pups, the drying and hardening of the parts resulting from this being supposed to stunt the growth. Even at the present time, it may be remarked, attempts are made to limit the growth of boys intended for jockeys by sweating. The practice of keeping dwarfs persisted through the Middle Ages into the eighteenth century. Lady Mary Wortley Montagu, when in Germany, found the dwarf a necessary appanage of every noble family. She describes the imperial dwarfs at Vienna "as ugly as devils," and, "bedaubed with diamonds." In these days dwarfs were not infrequently noted for their wit and wisdom, and, like the court jesters, whom in fact they superseded, were allowed unlimited freedom. It is said that one of the Danish kings actually made his dwarf prime minister in order to get at truths that other men were afraid to utter. Peter the Great, among other vagaries, was interested in dwarfs, and in 1710 gave a feast to celebrate the marriage of his favorite Valakoff with the dwarf of the Princess Prescove Feodorovna, at which seventy-two dwarfs of both sexes were present. The practice of keeping dwarfs was widespread, and has been immortalized in the canvases of some of the most celebrated painters, notably Velasquez, Raphael, Paul Veronese, Domenichino, and Mantegna. Their delineations are in some cases of much value in enabling us to determine the nature of the dwarfism known to former times. In fiction, too, the dwarf has played a prominent part, as readers of "Peveril of the Peak" and "The Black Dwarf" will remember.

Some personages, famous in history, have been of small or even diminutive size. Philetas, of Cos, tutor of Ptolemy Philadelphus, was, according to Ælian, so light as well as small that he was obliged to carry leaden weights in his pockets to prevent his being blown away. Others that might be mentioned are Atila the Scourge, Æsop the fabulist, Procopius, Gregory of Tours, Pepin le Bref, Prince Eugene, Admiral Gravina, Fleury and Garry the actors, Arendt the Danish antiquarian. In England the history of dwarfs is traceable to mythological times.

The origin of the almost generic title of "Tom Thumb" is to be found in an ancient ballad, which informs us that "In Arthur's court Tom Thumb did live." The most famous English dwarf was Sir Jeffery Hudson, who was born at Oakham in 1619. He made his first appeal to fame when he was presented by the Duchess of Buckingham to Queen Henrietta Maria as he dished out of a pie. From the age of eight till thirty he was only eighteen inches high, but afterward suddenly shot up to three feet nine. He became a well-known courtier and was entrusted with several matters of delicacy. He did not lack courage for he fought two duels, one with a turkey-cock, celebrated in the verses of Davenant, and another with Mr. Crofts, who came to the meeting with a squirt. A more serious encounter, however, followed, for little Jeffery, who was mounted on horseback to compensate for his inferior height, shot his opponent dead. He was twice made prisoner, once by the Dunkirkers as he was returning from France, and once by the Barbary pirates. On each occasion he was soon ransomed. He eventually, however, fell on evil days, for he was accused of participating in the popish plot and was sent to the Gate House, where he died in 1682.

About the same period, or somewhat earlier, Charles I. had a page at his court called Richard Gibson, who was remarkable for his small size, and was, appropriately enough, a miniature painter. He married Anne Shepherd, the dwarf of Henrietta Maria, the ceremony being performed by Edmund Waller. Together they only measured two inches over seven feet. Evelyn designated Gibson as a "compendium of a man," and the pair were painted hand in hand by Sir Peter Lely. Mistress Gibson had nine children, five of whom survived and were of normal size. She died at the age of eighty, and her husband at seventy-five.

One of the most celebrated dwarfs was a Polish gentleman, Joseph Borwilaski, who became noted throughout Europe as a handsome man, a wit, and something of a scholar. His parents were tall, but three of his brothers were small. He was born in 1739, and died at the advanced age of ninety-eight in the city of Durham, where, by the irony of fate, he is buried by the side of the Palstaffian Stephen Kemble. His height was thirty-nine inches. Diderot wrote a history of the family.

Another remarkable dwarf was Richebourg, a servant and pensioner of the Orléans family, who died in Paris at the age of ninety. He was only twenty-three inches high, and his diminutive size was taken advantage of during the stirring times of the Revolution when, masquerading as an infant in his nurse's arms, he carried despatches in and out of Paris.

Coming to more recent times we may mention Charles Stratton, or "Gen. Tom Thumb," one of the greatest of Barnum's successes. At birth he was above the normal weight of the new-born, but ceased to grow when five months old. His height at that time was less than twenty-one inches. He created a sensation in Europe and amassed a large fortune.

Perhaps the next most striking sensation has been the "Lilliputians," a troupe of singers and comedians possessing much talent as burlesquers. They were probably the same individuals who were examined by Joachimsthal in Germany.

Many of the recorded dwarfs have been very diminutive. Buffon mentions dwarfs only twenty-four, twenty-one, and eighteen inches high, and describes one who, when thirty-seven years old, measured sixteen inches, whom he considers to have been the smallest person on record. The "Princess Topaze," a French dwarf, is twenty-three and a half inches tall (or rather short?), who weighs only fourteen pounds. Her parents were of normal size.

On consideration of the facts recorded in the above remarks we are led to certain important conclusions. Most dwarfs have been well proportioned, without deformity, and of average or more than average intelligence. Some of them have been persons of great vigor and force of character. In fact they may be said to dif-

fer but little from ordinary individuals save in the one point of size.

Dwarfs fall naturally into two classes: Those that are diminutive at birth and subsequently develop slowly, so that they always remain more or less stunted; and those that are of normal or even more than normal size at birth and later cease to grow. Authentic information as to the size of dwarfs at birth is hard to obtain. We may, however, correctly infer that they are often below the average size, for dwarfed mothers have frequently borne children in a natural way, and physical considerations would preclude us from coming to any other conclusion. Conversely, normally developed mothers have not infrequently given birth to dwarf children. Instances are on record of new-born infants weighing a pound and three-quarters, or even less, at full term. The subsequent history, however, of these children is unfortunately often unknown. Home (Philosophical Transactions of the Royal Society of London, 1825) speaks of a child borne by a woman following the Duke of Wellington's baggage train, which weighed at birth only one pound, and measured between seven and eight inches long. At the age of nine it was only twenty-two inches high. This is said to be the same child, called Caroline Crachami, whose skeleton is in the museum of the Royal College of Surgeons near that of O'Byrne, the "Irish Giant."

Inasmuch as in the cases of dwarfism that we have so far been considering the parts are perfect in form and the limbs are in the normal proportion to the trunk, although the body as a whole is defective in size and weight, it has been suggested that here we really have to do with a condition of infantilism which may be defined as a state of imperfect and delayed development, whereby the individual preserves the characteristics of childhood long after these should have disappeared. This view is supported by the fact that in many cases of dwarfism the head is proportionately large, as it is in the infant, the genitalia are undeveloped, and the signs of puberty are absent or delayed. Joachimsthal (*Deutsche med. Woch.*, 1899, xxv., SS. 269-271, 288-290), studying with the Roentgen rays a troupe of exhibiting lilliputians, found that bone formation was imperfect, the various centres of ossification being strictly comparable to those of a child, although the individuals in question were about thirty years of age. Undoubtedly, in some at least of the deficiencies complete development and function may eventually be attained. For instance, many of these dwarfs have proved themselves capable of propagating their kind. One cannot fail to be struck also with the fact that dwarfs frequently reach an advanced age, the reverse of what is found in the case of that other contrasting anomaly of development, gigantism. This suggests certainly not a defect in the vitality of the body as a whole, but rather an anomaly in the nature and direction of the growth. The normal balance between structure and function is upset and the individual may possess the mind and faculties of the adult in the body of the child.

With regard to the etiological factors at work in the production of dwarfism we are compelled to admit that our knowledge is far from complete. Our views therefore must partake largely of the nature of hypotheses. Up to the present time but few cases of dwarfism have been studied, and it is chiefly upon the facts gleaned from these and the results of experimentation that our inferences must be drawn.

The condition of dwarfism is clearly but one aspect of the larger question of dystrophy or dysgenesis. Consequently it can be apprehended only by a reference to the elementary principles governing the formation and growth of tissues.

The developmental forces concerned in the elaboration of a new individual may be inadequate to bring the process to completion. If they are totally inadequate, death of the embryo results. Short of this extreme result, however, the nutritional processes may be so modified that we get a deficiency or excess in growth of the organism, either in part or as a whole, or they may be so perverted

that we have actual malformation and deformity. There is, therefore, a close relationship between dwarfism, gigantism, malformations, and monstrous births. The peculiarities of development that result in such anomalies may be inherent in the sperm cell or ovum or both, and in this sense are inherited, or they may be due to causes operating on the ovum subsequently to fertilization, either before (intra-uterine acquired causes) or after birth (post-natal acquired causes). We have, therefore, to take into account primitive peculiarities of cell substance on the one hand, and external causes, nutritional or mechanical, acting on the fruit, on the other.

In this particular certain general considerations are worth noting. Thoma ("Untersuchungen über die Grösse und das Gewicht der anatomischen Bestandtheile des menschlichen Körpers im gesunden und im kranken Zustande," Leipzig, 1882) has called attention to what might be called a general "law of deviation." In adults the normal length of the body is on an average 169 cm. in the male and 163 cm. in the female, while the average weight is 60 kgm. and 56 kgm. respectively. Considerable variations on either side of this norm may occur. Taking a large number of individuals, in one-half the amount of deviation will be anywhere between 0.0 and 3.8 cm. In accordance with the law he has formulated, the fifth multiple of this figure when added to or subtracted from the normal average height will give the outside limit of giant or dwarf growth, and will be reached only once in every thousand cases. According to this an adult would be regarded as a dwarf if the height fell below 163 minus 19 cm., or 144 cm. Similarly 5 kgm. is the approximate aberration in weight from the normal in the adult. The fifth multiple of this, 25 kgm., subtracted from 56, gives 31 as the upper limit in weight for dwarf growth. With regard to weight, we have, of course, to be careful to exclude such conditions as marasmus and loss of height from spinal disease. In the case of the new-born the normal average in length is 50 cm. and the weight 3.2 kgm. The amount of deviation is approximately 1.4 for length and 0.28 for weight. The upper limit for dwarf growth in mature infants at birth would therefore be 43 cm. and 1.8 kgm. respectively. Some allowance for individual peculiarities must be made, for many children that are diminutive at birth make up for the deficiency by rapid growth afterward, while, again, some children that are normal in size and weight at birth subsequently become retarded in their growth and development. This "law," while it gives us convenient data for classification, is, needless to say, very far from being an explanation of the anomaly.

Again, certain adventitious circumstances, acting apparently on the germinal cells, may play a part. It has long been known to stock-raisers that continued in-breeding will result in the production of diminutive offspring. And it is said that after Napoleon's campaigns there was a diminution of from one to two inches in the stature of the French people. This has been attributed to the fact that the strongest and best developed males were drawn for military service, but, no doubt, poverty, famine, and disease, affecting the people as a whole, were important factors. These observations suggest that defective physical development on the part of one or both progenitors may lead to insufficient vitality, or what might be termed "relative vegetative inertia" on the part of the germinal cells. This leads us to the consideration of the importance of heredity in this connection.

The inheritance of a developmental anomaly is well illustrated in the case of polydactylism. This peculiarity has been known to persist for three, four, or even five generations, although it may in time be eradicated by marriage with normal persons. The Foldi family, belonging to the Arabian tribe of Hyabites, all have twenty-four digits. They never marry outside the family, and the anomaly is so constant that any child having the normal number of digits is put to death as the offspring of adultery. Reference will be made later to the influence of pressure of the amniotic sac upon the growing embryo in the production of this and other deformi-

ties, but it would be absurd to suppose that such a cause could be present throughout several generations and in a whole race. We are driven to conclude that there must have been some anomaly in the formation and development of the "Anlage" arising in the earlier stages of embryonic life. This being so, it would not be surprising to find the influence of heredity somewhat marked in the condition of dwarfism. As a matter of fact, dwarfism is not invariably an expression of a hereditary peculiarity, although sporadic cases may occur in several generations derived from the same stock. Certain parents nevertheless seem to have a tendency to produce dwarfs. To cite only one example, the celebrated Borwilaski had a brother and sister who were dwarfed. The fact, however, that while certain members of a family may be dwarfs, others may be normally developed indicates that the cause, whatever it be, is not a constantly acting one, or else that there are a number of factors which must be correlated before the given result will take place. That the issues involved may be very complex is well illustrated by an extraordinary instance related by Ekman ("Dissertatio medica descriptionem et casus aliquot osteomalaciæ sistens," Upsaliæ, 1788) where dwarfism and osteopsathyrosis were associated through three generations. The ancestor could not walk because of deformity. He had four children, of whom one son was a dwarf and one daughter was small and deformed. This son begat by a healthy wife a son who had curved extremities, and was liable to fractures on the slightest provocation. This son in turn married a healthy woman who gave birth to a son who had so many fractures that when he reached adult life he could not move, and a daughter who was dwarfed and also suffered from multiple fractures in childhood. Apparently, then, heredity may manifest itself, not only in the rate and amount of growth, but also in the structure and composition of the tissues. Moreover, these two factors, simple growth and organic formation, are not always correlated, and may even be antagonistic. Numerous exceptions to hereditary transmission, however, occur, for when both parents have been dwarfs, the offspring have frequently proved to be normal in size and proportion. What, however, is an occasional anomaly in the case of civilized peoples is a constant racial characteristic in certain of the African tribes, such as the Akkas and Bushmen. This can hardly be explained on any other assumption than that an acquired peculiarity, due to unfavorable environment, has become transmitted and in time impressed upon a great number of individuals, unless we are prepared to accept the other alternative that all races of mankind were originally much smaller than they are at present, and, owing to natural selection and the growth of civilization, gradually developed into a superior organization, a view that, at all events, is not supported by history or tradition. Heredity probably has the same bearing in dwarfism as it has in the case of other anomalies; no more and no less.

The influence of extraneous circumstances on the vegetative power of the germinal cells is well illustrated by some comparatively recent and most suggestive experiments.

In experimenting with the fertilized eggs of some of the humbler forms of life, Roux showed that if, in the two-cell stage, one of the blastomeres be destroyed, the other will regenerate the missing half and eventually give rise to a complete embryo. Endres, Walter, and Morgan have come to similar conclusions in the case of the frog, with the additional observation that the peculiarity is characteristic of the earliest stages only and may be entirely suppressed. In 1891 Driesch separated, by shaking, the blastomeres of the sea urchin's egg when in the two- and the four-cell stage. Blastomeres thus separated produced in time a complete blastula, and the resulting gastrula was a perfectly formed dwarf of one-half or one-quarter the natural size, as the case might be. Zoja, too, in some remarkable experiments on the medusa was able to produce dwarfs one-sixteenth of the normal size. Morgan has further discovered the important fact that

either a half embryo or a complete half sized dwarf will result according to the position of the blastomere. If, after one blastomere is destroyed, the other be allowed to retain its normal position a half embryo is always produced, as Roux had already shown. If, however, the blastomere be inverted, it gives rise either to a half embryo or a whole dwarf. In this connection we might recall certain early experiments of Saint Hilaire, who produced dwarf chickens by shaking the egg in the direction of its long axis. Thus it would appear that a rearrangement of the cell material may restore that equilibrium of the entire ovum necessary for the production of a whole embryo. This extraordinary power is, however, less marked in the higher forms and is ultimately lost. In view of the fact, however, that parthenogenesis, which is a constant occurrence in some of the lower forms of life, is sometimes to be observed even in such a highly organized creature as the hen, and in fact has been advanced by some authorities to explain the development of certain tumors of the human ovary, it is not impossible that anomalies in the segmentation of the ovum in human beings, may, although rarely, give rise to one type of dwarf at least, namely, that dwarfed from birth. Two factors would appear to be necessary: some cause to blight one-half of the ovum in the very earliest stage of its development, and another producing a disturbance of the cell equilibrium. As to what these factors may be, whether developmental, traumatic, or inflammatory, we have absolutely no information. One or two facts may possibly point us in the right direction. Malposition of the fertilized ovum as a whole may be brought about by intratubal and intra-uterine inflammation, instances of this being tubal gestation and placenta previa. It is not inconceivable, therefore, that endometritis and deciduitis might lead to blighting of a portion of the embryo and disturbance of protoplasmic equilibrium. That a modification of external conditions does have a profound effect on the developing ovum, in some animals at least, we have ample proof. Darest, by incubating hen's eggs at a temperature more elevated than that usually employed, got early development and dwarf formation. Gerlach and Koch ("Ueber die Produktion von Zwergbildungen im Hühnerrei auf experim. Wege," *Biol. Centralbl.*, xxii., 1894) also obtained a retardation of development and dwarf growth by varnishing eggs so as to exclude all but a small amount of air.

The effect of primitive peculiarities inherent in the germinal cells in producing developmental anomalies of the Anlage has already been noted in regard to polydactylism, and it is now pertinent to inquire in how far deficiencies in the formation of those structures more especially concerned in the general maintenance of nutrition, namely, the cardiovascular and nervous systems, and the thyroid gland, are of importance in the production of dwarfism.

If the circulatory apparatus be deficient either in the size and extent of the vessels or in the formation of the chambers and valves of the heart, it is obvious that the circulation of the blood must be inadequate for the needs of the organism, which consequently may be inhibited in its growth. Long ago Virchow pointed out the association of cardiovascular hypoplasia with other developmental defects, such as scanty production of the pubic hair and small size of the genitalia, conditions that may be regarded as manifestations of partial infantilism, if we take the view of Hertoghe, that there is such a thing as partial infantilism ("Die Rolle der Schilddrüse bei Stillstand und Hemmung des Wachstums und der Entwicklung," Spiegelberg, München, 1900). Gilbert and Rathery (*Presse méd.*, May 7th, 1900) have, it may be mentioned, found a moderate grade of dwarfism in some cases of mitral stenosis.

With regard to the influence of the nervous system in the production of dwarf growth the available evidence is not conclusive. The close relationship of the central nervous system to the nutrition of the tissues is of course admitted by everybody, and we are aware how often injuries to certain ganglion cells or nerve trunks are fol-

lowed by atrophy or other degenerative disturbance. It would not be surprising, then, to find that a defective development of the central nervous system might lead to aplasia or hypoplasia in the embryo. Of course the more extensive defects of the central nervous system, as anencephaly and amyelinia, are incompatible with life, and consequently cannot be adduced as conclusive evidence on the subject of dwarfism. As a matter of fact, however, whatever information we possess seems to negative the position that dwarfism is a neurotrophic disorder. For instance, as Cruveilhier has shown, the most extensive hydranencephaly may exist without a trace of defective development in the rest of the body, and Vogt, Klebs, and Aeby have pointed out that in microcephaly the individual as a whole may in other respects be well developed. The most we can say is that certain forms of local hypoplasia may with some probability be referred to central nervous disturbances. The probability is increased when in a child with such a defect the process extends subsequently, as in a case recorded by Emminghaus (*Deutsches Archiv f. klin. Med.*, Bd. ii., S. 96, u. Bd. xii., S. 49), where there was congenital microplasia of one arm followed in the tenth year by a trophoneurosis of the eye and corresponding side of the face.

That the thyroid gland exerts an important and often controlling influence in the processes of nutrition cannot now be denied. In how far athyroidia has to do with dwarfism is still a moot point. The whole question as to the relationship of the thyroid gland to myxœdema, cretinism, and deficient development generally will be dealt with more at length shortly. Suffice it to say here that there is considerable evidence to support the view that there are many minor forms of cretinism in which the most striking and characteristic features are absent, and where the analogies to dwarfism are close. Küster extirpated the thyroid gland in a boy of fourteen, whose growth was thereby arrested so that he always retained the characteristics of a boy of that age. Eiselsberg (*Langenbeck's Archiv*, Bd. xlix., 1895) removed the thyroid in two lambs a week old. At the end of six months they weighed 10 and 14 kgm. respectively, while the controls weighed 35 kgm. The disturbance was general and involved the brain as well as the skeleton. Kappeler also found in a boy of twelve and a half years, who had been deprived of the gland, that he did not grow and developed some of the symptoms of myxœdema. It may well be, therefore, that infantilism, as Brissaud holds (*Leçons sur les maladies nerveuses*, Paris, 1895), is simply an attenuated form of cretinism. Additional support is given to this view by the fact that some of the cases have been improved by thyroid feeding. Cases of this kind have been recorded by Wunderlich (*British Med. Journ.*, ii., p. 1420, 1897) and Dukes (*British Med. Journ.*, i., p. 618, 1898). In Wunderlich's case palpation proved the thyroid to be extremely small. In this connection also should be cited an interesting case of Sulzer's (*Deutsche Zeitschrift f. Chirurgie*, 1893) in which a goitrous thyroid was removed from a boy twelve and a half years of age. In five years he was a typical cretin. He then began to improve and in four years had regained the normal condition. It was found that a portion of the gland had been left behind at the operation, and that this portion began to grow some eight years afterward. In the same way the compensatory development of an accessory thyroid has an important bearing on the question of cretinism. These facts afford a probable explanation for such curious cases as that of Sir Jeffery Hudson, who, as we have seen, after remaining eighteen inches high for twenty-two years, suddenly shot up to three feet nine inches. Even if we are prepared to admit that infantilism is due to athyroidia, the identity of infantilism with dwarfism is not beyond cavil. At most can we say that the explanation may hold good for some of the cases. For, as Lorain was the first to point out, instances are met with in which there is no disturbance of the thyroid gland, and the defect in size is not true infantilism, but rather to be attributed to premature epiphyseal ossification.

So far we have been discussing the relationship of defective organization of the "Anlage" of the various systems to the question of general hypoplasia.

We pass on now to the question of intra-uterine malnutrition. In this connection ill health or improper diet affecting the mother or a local anomaly of placentation is the chief factor concerned. The former act by bringing a poor quality of blood to the support of the fetus, and the latter presents a hindrance to the free interchange that should go on between the maternal and fetal bloods. The existence of syphilis, tuberculosis, or chronic alcoholism in the mother might be expected to produce its effect upon the offspring, largely in the form of lowered vitality and increased susceptibility to disease. It is suggestive in this connection that the Japanese are in the habit of producing dwarf pups by feeding the mothers with alcohol. Charrin, furthermore, could produce a similar result by the injection of ptomaines. Yet the children of mothers the subjects of long-standing disease or cachexias are by no means always diminutive or poorly nourished. The vitium shows itself, not so much in immediate anomalies of physical development, as in disordered function and defective reserve power. Much discussion has centred round the question as to whether there is such a thing as fetal rickets. Rickets generally makes its appearance during the first or second year of life, after the sixth month, and is commonly attributed to insufficient and improper alimentation, although unhygienic surroundings may also play a part. It is not impossible that analogous causes, operating during intra-uterine life, might produce the same effects. Rickets is not hereditary, although congenital influences may play a part. In former times, and indeed to a large extent even in these days, the term "fetal rickets" has been used in a very loose way to include several affections characterized by imperfect bone formation, such as syphilis, osteogenesis imperfecta, and chondrodystrophia fetalis, which are now, thanks to recent studies, separated fairly well one from the other. It is now the general consensus of opinion that congenital rickets, in the sense of a rickets that has run its course previous to birth, does not exist. To this, however, we shall return.

In one or two cases the study of dwarf foetuses has revealed the fact that there is an abnormal relationship between the foetal placenta and the maternal structures. The chorionic villi were scanty and were composed of thin strands of connective tissue covered by an abnormally thick layer of epithelium, while at the same time the projections of the maternal decidua did not extend through the thickness of the foetal placenta, as is usually the case. The explanation of this that has been offered is that there was a defective development of the decidua, but this is almost certainly incorrect. Chipman (*Observations on the Placenta of the Rabbit*, "Studies from the Royal Victoria Hospital," Montreal, vol. iv., December, 1902) has shown that the more intimate connection between the foetal and maternal parts is brought about by a process of absorption, the ectodermal cells of the chorionic villi proliferating and invading the openings of the uterine glands and extending along the sheaths of the blood-vessels. The maternal tissues are thus eroded as it were, and are quite passive in the matter. It may well be, then, that such an anomalous development of the placenta is due, not to malnutrition and imperfect cell growth on the part of the mother, but to a primary fault in the growing embryo that evidences itself in an imperfect development of the placenta. Apparently, however, before such an abnormality can result in dwarfing of the fruit it must be quite extensive, for the given result does not always follow. As Langhans has pointed out, a similar peculiarity of placentation occurs in cases of tubal gestation, where the fetus is usually well developed.

Further, the proper interchange of blood and nutriment through the placenta may be gravely interfered with owing to inflammatory disturbances. Here syphilis plays a leading rôle. As is well known, in syphilis hereditaria tarda there is a delayed development of the bony and muscular systems, so that a young man of twenty

ay look like a boy of ten or twelve. With this there is an infantile condition of the genitalia and the hair of the pubes and other parts is slow in appearing. The characteristic lesion of syphilis in the placenta is endarteritis, which leads to extensive destruction of the vascular area, with degeneration, atrophy, and fibrosis of the region involved. The placental circulation must in such cases be greatly interfered with. In syphilis, however, other factors enter. We have to admit that the presence of so serious a disease in the parent, usually the mother, must have a tendency to lessen the vitality of the germ cell, to say nothing of the presence of the germ of the disease (the existence of which on analogy can hardly be denied) in the fertilized ovum, with all that this implies.

Hitherto we have been discussing what might be called *primary* or *essential* dwarfism (microsomia) in which the redominating element is a deficiency in the vegetative energy of the cells. The affected persons are in fact normal individuals save in the one particular of size and weight. Besides this, however, we have to recognize another class of cases that clearly belong to a different category. I refer to instances of *secondary* or *symptomatic* dwarfism. Here, while the height of the body is below the normal, the weight is not so strikingly diminished as in the true dwarfs. The main feature is, however, that in addition to general hypoplasia, there are evidences of pathological changes in the tissues, particularly in the bones, leading to asymmetry, deformities, fractures, or malformations. The defects are structural as well as nutritional. Just at this point it may be remarked that the exact nature of these cases presents one of the most difficult problems in etiology. In former times many cases of congenital dwarfism of this type were put down to syphilis, rickets, or cretinism. It was soon found, however, that there were some important points of distinction between certain of the cases. The typical features of cretinism were not always present, nor did the disease, if rickets, conform to the picture of the ordinary post-natal affection. These considerations have led investigators to recognize several distinct types, which are by some regarded as separate entities. We have, therefore, to consider in this connection rachitis, cretinism, osteopsathyrosis, chondrodystrophia foetalis, and osteogenesis imperfecta, affections that agree in this at least with more or less stunting of the body there are structural modifications of the bones of an obviously pathological nature. The amount of confusion that has involved the subject is sufficiently indicated by the number of names that have been proposed for the condition—retal rachitis, pseudorachitism, cretinoid dysplasia, chondritis foetalis, micromelia chondromalacia, achonroplasia, chondrodystrophia foetalis. A decided step in advance has been made through the researches of Kaufmann ("Untersuchungen über die sogen. foetale Rachitis," Berlin, 1892, u. Ziegler's "Beiträge," 1893, xiii., S. 2-64) who introduced the name chondrodystrophia foetalis. Here the type of dwarfism is micromelic and the lesions are usually symmetrical. The body is plump, the micromelia rhizomelic, the head large, and the hands often show the so-called "trident" deformity. There are, however, notable differences in the length, curvature, and consistence of the bones of the extremities, and in the configuration of the skull. Kaufmann, consequently, recognizes two groups: one, in which there is a distinct cretinoid appearance of the skull and face, namely, a deeply sunken nose, prominent eyelids and lips, thick cheeks, and large mouth; and another, in which the nose is flattened and retracted as a whole. In the former type the bone is of good consistence although somewhat more vascular than normal, while in the latter the bone is soft. No hard-and-fast line can be drawn between the two forms, and Kaufmann regards them as manifestations of the same process, the differences being due to the chronicity and intensity of the process. The retraction of the root of the nose is usually said to be brought about by premature ossification and synostosis of the os tribasilare. The ethmoid is also somewhat

shortened, and in some cases may be the only part affected. Klein has observed well-marked craniotabes in some cases. In some, too, there may be beading at the costochondral articulations, and defective development of the pelvis, glenoid, and cotyloid cavities. Lordosis may also be a marked feature, and Regnault (*Bull. et mém. de la Soc. d'Anat.*, 1901, lxxvi., pp. 559-560) has found the vertebrae involved. The disease begins in fetal life, running its course usually, as it is believed, from the third to the sixth week. As a consequence the bones affected are the base of the skull, the long bones, the ribs, and the pelvis. The bones formed in membrane, those that in late fetal life are mainly cartilaginous, usually escape. Kaufmann has described three sub-classes in chondrodystrophia: Chondrodystrophia malacica, in which the bone is soft; C. hypoplastica, in which there are evidences of retarded growth; and the C. hyperplastica in which the epiphyseal ends of the long bones are greatly enlarged. The periosteal ossification is normal, so that the bones become plump and thick, although somewhat irregular, but the growth in length is disturbed owing to faulty ossification at the epiphyseal junctures. Ingrowth of the periosteum at the epiphyseal lines may occur. Microscopically the cartilage cells are deficient in growth, being spindle-shaped and irregularly arranged, while the hyaline matrix is more or less soft and homogeneous. It is not improbable, however, although the majority of children thus affected are stillborn, that when the affection is of mild type or arises late on in fetal life, existence may be prolonged for some time. Parrot has met with an example in a child seven and a half years old, who measured 94 cm. in length. Certain changes in the bones of the hands, notably in the fingers, seem to prove that the disturbances of ossification may go on at a later period than that above indicated. (See Thompson, *Edin. Med. Journ.*, 1892-93, vol. xxxviii., pp. 1109-1113, and Turner, *Practitioner*, 1899, vol. lxi., pp. 263-277.) Thompson (*loc. cit.*) has met with two instances at the ages of thirty-six and thirty-nine, and others have been described by Osler (*Trans. Amer. Cong. Phy. and Surg.*, 1897, vol. iv., pp. 190-192), Abt (*Archives of Pediatrics*, Cestan, "Nouvelle Iconographie de la Salpêtrière," 1901, xiv., 277-289), Apert (*Ibid.*, pp. 290-298), and Baldwin (*Medical News*, 1890, vol. lvii., pp. 138-141).

The exact relationship of the disease, called by Vrolik and Stilling (*Virch. Archiv*, 1899, cxv., SS. 357-370) osteogenesis imperfecta, to chondrodystrophia, is still *sub judice*. The studies of Stilling, Hildebrandt (*Virch. Archiv*, 1899, clviii., SS. 426-444), and Harbitz (Ziegler's "Beiträge," 1901, xxx., SS. 605-628) go to show that it is a definite intra-uterine process. There is clearly some defect in the process of ossification, for the bones are soft and brittle, with the result that fractures and deformities are common. Microscopical study has shown that the trabeculae are few in number, irregular, and imperfectly formed. There is no continuous system of trabeculae with Haversian canals and lamellae as in normal bone. A point of great interest is the extraordinary manner of ossification of the skull. The calvarium is formed not of continuous bony plates, but of a multitude of small mosaics, sometimes touching one another, but also attached by bridges of periosteum and dura. In a remarkable case described by Stilling, the cranial covering consisted of a membranous sac which contained scattered bony spicules. So far as is known there is no synostosis of the basal synchondrosis in this disease. While the affection has hitherto been found only in the new-born or in very young infants, it is not necessarily fatal, and Harbitz is inclined to think that some cases of dwarfism that have been regarded as examples of fetal rickets or chondrodystrophia may have been osteogenesis imperfecta. As in chondrodystrophia porosity of the bones occasionally appears to depend on hereditary conditions, and Bircher (Lubarsch u. Ostertag, "Allg. Aetiologie," Wiesbaden, 1896, S. 53) has found osteoporosis in the case of a chondrodystrophic dwarf (cf. also the case of Ekmann, referred to above). We are, therefore, not prepared to

believe with Paltauf ("Ueber den Zwergwuchs," Wien, 1891) that the two affections are not related.

To rickets chondrodystrophia bears much resemblance, although there are several differences. In both there is enlargement of the epiphyseal ends of the long bones (chondrodystrophia hyperplastica), the long bones may be curved, the ribs beaded, and there may be spinal and pelvic deformities. In rickets, however, the arms are usually long. Periosteal bone formation is also interfered with. The periosteum is readily stripped off and the underlying bone is softer and more spongy than normal. As the condition heals the bone becomes unusually plump and dense. Basilar synostosis does not occur in rickets. Microscopic study has shown that the epiphyseal zone of proliferation in rickets is thicker than normal, irregular in outline, soft, and very hyperæmic, so much so that Kasowitz believed the lesions to be of inflammatory origin.

The microscopical appearances of the growing ends of the bones in chondrodystrophia are, however, quite different from those in post-natal rickets. No clear evidence of the existence of rickets originating during intra-uterine life is forthcoming, yet there is a parallel between chondrodystrophia and rickets, for, as is well known, post-natal rickets, if severe, results in the stunting of the growth of the affected individual, and cases of extreme dwarfism have been met with. The lesions are characteristic. The skull is large, although the face is relatively small. The fontanels remain open for a prolonged period, and bone in certain regions, especially the occipito-parietal, may be so thin as to give way under the pressure of the finger (craniotabes). The forehead is usually large and square, owing to the formation of flat hyperostoses over the frontal eminences. The sternum projects and the sides of the chest are drawn in (pectus carinatum). The spine is often curved and the extremities become greatly deformed owing to the weight of the body and muscular action. The pelvis is contracted; dentition is delayed and the teeth are small and badly formed. The condition is by many believed to be due to infection or possibly auto-intoxication. This view is supported by the experiments of Mörpurgo (*Centralbl. f. Path.*, 1902, xiii., S. 113), who showed that rickety changes in the skeletons of young white rats could be produced by the injection of cultures of a diplococcus. The lesions in rickets, however, are so unlike those of chondrodystrophia in important particulars that it is unlikely that an infective cause is at work in the latter disease. Differentiation between chondrodystrophia and rickets may be made by attention to the following points: The dwarfism in the former is micromelic; in the latter not. Periosteal bone formation is not interfered with in chondrodystrophia, while it is in rickets. In healed rickets the bone is abnormally dense; not so in chondrodystrophia. Basilar synostosis does not occur in rickets. In rickets you do not get "trident deformity" of the hands. Developmental anomalies, like cleft palate and polydactylism, are not found in rickets. Osteogenesis imperfecta is recognized by the fragility of the bones, the peculiar ossification of the cranium, and the lack of basilar synostosis.

It is a suggestive and a striking fact that while we are able to draw these distinctions between the type cases of chondrodystrophia, osteogenesis imperfecta, and rickets, there exist borderland cases in which some of the features of these diseases may be combined. Such a one is that reported by Hektoen ("Anatomical Study of a Short-limbed Dwarf," *Amer. Jour. Med. Scien.*, May, 1903), in which in a micromelic dwarf, forty-five years of age, there were one hundred and seventy-two Wormian bones in the skull, without premature synostosis of the os tribasilar, with shortness and curvatures of the long bones, enlargement of the articular ends, curvatures of the spine, deformity of the pelvis, osteoporosis and multiple fractures, and a fibroid thyroid. A case presenting features both of chondrodystrophia and osteogenesis imperfecta has been described also by the Countess von Geldern-Egmond ("Beitr. zur Casuistik der sogen. fötalen Rachitis," *Inaug.-Diss.*, Zurich, 1897).

The etiology of these interesting conditions is still largely unknown. Heredity appears to be a factor in some cases. In one case, recorded by Porak ("Beitrag zur Histologie und Funktion der Schilddrüse," *Inaug.-Diss.*, Königsberg, 1892) a dwarf gave birth to one healthy child and a second with all the signs of the so-called "fœtal rickets." Guéniot (*Bull. et mém. de la Soc. Obstet. et gynéc. de Paris*, January, 1893) recounts the operation of Cæsarean section on an achondroplastic dwarf, the child being similarly affected. The parents of chondrodystrophic dwarfs as well as their children are nevertheless often healthy. Heredity seems then to play a minor rôle. The influence of heredity in the case of polydactyly has already been dwelt upon, and it is a curious fact that polydactyly may sometimes be associated with dwarfism. An instance of this will be found in *Hutchinson's Archives of Surgery* for April, 1893, where there is given an illustration of a micromelic polydactylous dwarf, copied from Theodore Kerckring's "Spicilegium Anatomicum," published in 1670. The drawing is not entirely to be relied upon, but it is clear that the limbs were too short for the trunk. Both the hands have seven digits; the right foot has eight and the left nine. The condition is not perfectly symmetrical, for in some cases two of the metacarpal or metatarsal bones are welded together. The long bones are plump, and, so far as it is safe to judge from the imperfect sketch, the ends appear to have been enlarged. The orbits are deformed, the two halves of the lower jaw are already united, and the ribs are short and badly formed. It is clear that here we have an abnormality of development in few respects comparable to rickets. It may be that here, as in simple polydactylism, we are dealing with a primary vitium of development inherent in the germinal cell. This view is supported also by the observation of Kirchberg and Marchand (Ziegler's "Beitr. zur path. Anatomie," Bd. v., 1889), who found cleft palate in a chondrodystrophic infant. One of Bowlby's cases, also, reported as congenital cretinism but really an instance of chondrodystrophia, had a cleft palate and a deformed nose. The right foot had six metatarsal bones but seven toes; the left foot had seven toes.

There is, however, another possible explanation. Recent observations have shown that many forms of hypoplasia, non-closure of sutures, and, in fact, the most extreme deformities may result from intra-uterine pressure. The simple weight of a limb resting on a band has been sufficient to erode the soft tissues to the bone. Twisting of the cord about a limb may lead to dwarfing or amputation. The pressure of bands traversing the amniotic sac is also a well-recognized cause of even more extreme deformities, such as anencephaly and cranio-rachischisis. Daresté believed that a contracted amnion was an important cause of hypoplasia.

In Klebs' text-book of "General Pathology" (vol. ii., 1889, Jena) is an interesting illustration representing a microscopical section through the proliferating end of one of the long bones in a micromelic dwarf. The growing cartilage cells are closely packed together, flattened, with their long axes at right angles to the long axis of the bone. The appearances could not be due to alterations in the ground substance which seemed to be normal, but could be attributed only to the effects of external pressure. This would, of course, lead to inhibited and imperfect ossification. The effects of intra-uterine compression are well illustrated by the experiments of Fol and Warynski (Thèse de Genève), who brought external pressure to bear upon a growing embryo. They found that the head was the part most amenable to pressure, and could to some extent be restrained in its growth. Warynski, also, by exerting pressure at the site of fusion of the two primitive cardiac rudiments, was able to produce a double-hearted monster. Klebs (*loc. cit.*, p. 306) refers to a most remarkable case in which a contracted sac led to a singular malformation. In an ectopic gestation the fœtus was found in a tight sac within the transverse mesocolon. There was syndactylism in the upper extremities and polydactylism in the lower. From the

recorded cases it would appear that contraction of the amnion does not lead to dwarfing of the fetus as a whole, but that certain parts are more liable to be affected, as the extremities and head. In this connection also may be remembered the fact that hydramnios is apt to be associated with grave deformities, such as exencephaly and spina bifida, and has been found in a case of osteogenesis imperfecta. The effect of intra-uterine pressure has also been emphasized by von Franqué ("Ueber sogenannt. fötale Rachitis," Sitzungsberichte der physikalisch-mediz. Gesellsch., Würzburg, Jahrg. 1893, S. 80).

It is on the ground of the obvious errors in development which are sometimes associated with chondrodystrophia, and which can only be referred to peculiarities of the Anlage, that Virchow objects to the term chondrodystrophia introduced by Kaufmann. Virchow points out that the condition imperceptibly shades into a pronounced developmental anomaly (*Missbildung*), which is finally represented by the phakomelia of Saint Hilaire.

The small stature, the peculiar facial configuration, and the enfeeblement of mental power, with other minor abnormalities found in some cases of chondrodystrophia, have induced the suspicion that some of these cases of dwarfism are really cases of cretinism. The difficulties in the way of differential diagnosis are great. Thus Dolega, Bernard, and Bircher have pronounced certain cases to be instances of cretinism, and yet a subsequent examination proved them to be Kaufmann's chondrodystrophia, and conversely, Neumann, Scholz, and others have described instances of cretinism as fetal rickets. The difficulties in the way will be readily comprehended if one considers for a moment the lesions in a typical case of cretinism. In the cretin the stature is almost always stunted, Maffei in twenty-two cases out of twenty-five finding the height to be less than 140 cm., while several were under 95 cm. The limbs and trunk are disproportionate. The head is usually relatively large, the top flat, and the occiput prominent, although microcephaly has been found. The fontanels and sutures remain open for a long time. The root of the nose is retracted, and the organ is short and thick with large wide nostrils. The lips and tongue are enlarged. The teeth appear late and are large. The first dentition usually persists throughout life. There is as a rule no hair on the pubes and in the axillæ. The sexual organs are poorly developed, and puberty, if it occur at all, is late. With regard to the finer structure of the bones in cretins, Langhans (*Vireh. Archiv*, 1892, cxxviii.) found that the cartilage cells were small, spindle-shaped, and anomalously arranged, being longitudinal to the axis of the columns. The rows were also often interrupted. The bony trabeculae were shortened and the marrow spaces in the

youngest portions of the bone were large and widely separated. The resemblance to Class I. of Kaufmann's chondrodystrophia is close. Typical cretinism is endemic and associated with goitre. Chondrodystrophic dwarfism is sporadic. Can, then, chondrodystrophia be sporadic cretinism? The recorded cases of chondrodystrophia go to show that the disease is of intra-uterine origin, and so far no evidence is forthcoming to prove that the affection ever arises subsequently to birth. Cretinism is said to be congenital in some cases, but the symptoms usually appear some five to eight months after birth, or even later. It is now believed that the changes in the skeleton of cretins are due to delayed ossification of the cartilages. Hofmeister (*Fortschritte auf dem Gebiete der Röntgen-Strahlen*, Bd. i., Hft. i., 1897), studying a case of cretinism with the x-rays, found that the epiphyseal ends of the bones grew slowly, and that the epiphyseal plates persisted for a long time. The bones were small. Ossification may in time be completed, but the process may take years; in fact, cretins may continue to grow until they are thirty or forty years of age. Periosteal osteogenesis is normal, or may be in excess. The peculiar appearance of the nose is due to premature synostosis of the bones at the base of the skull, although, as Niepe, Stahl, and Klebs have shown, this anomaly of bone formation does not always occur.

The stunted growth is believed by Bircher (*loc. cit.*) to be due to defective development of the cartilage cells, as was found occasionally by Virchow and Klebs at the base of the skull. We find, therefore, that cretinism and the so-called chondrodystrophia have much in common. The resemblance can, however, be made out clearly only in the case of chondrodystrophia of Kaufmann's first group. Cretinoid chondrodystrophia might be explained as cretinism that had become marked at a very early period of intra-uterine life.

Further information might be obtained by an inquiry into the condition of the thyroid gland in chondrodystrophia. Hofmeister ("Experimentelle Untersuchungen über die Folgen des Schilddrüsenverlustes," *Beiträge zur klin. Chirurgie*, 1894) holds that the changes in the bones produced by thyroidectomizing rabbits are identical with those found in chondrodystrophia as described by Kaufmann, H. Müller, Kirchberg, and Marchand. Although we must admit the great similarity of the lesions in the two cases, this, of course, does not prove identity. Leblanc (*Comptes rend. de Soc. de Biol.*, 1902, liv., 88-89) states that chondrodystrophia is often associated with myxœdema and that disturbance of the thyroid is the *causa morbi*. Nasan (*Rév. de Neurologie*, 1901, p. 549) is of the same opinion. There is no need of entering here into the question of the identity of myxœdema and

Case.	Observer.	Type of Disease.	Thyroid.	Reference.
I..	Bowlby	Cretinoid with some signs of myxœdema.	Absent	Trans. Path. Soc., 1884, p. 450.
II..	Kirchberg and Marchand.	Not cretinoid	Not enlarged	Ziegler's "Beiträge zur path. Anat.," Bd. 5, 1889.
III..	Dolega	Cretinoid	A few atrophied remains without colloid found.	Ziegler's "Beitr. zur path. Anat.," Bd. 9, 1891.
IV..	Paltauf	Very small	"Ueber den Zwergwuchs," Wien, 1891.
V..	His (quoted by Paltauf).	Apparently normal.
VI..	Bernard	Cretinoid	Thyroid absent, but a very small accessory found.	"Die Cretine Pohl," Inaug.-Diss. Würzburg, 1892.
VII-XIX.	Kaufmann	Eight cretinoid	Small in two; without change or at least not enlarged in five.	"Untersuchungen über die sogenannte fötale Rachitis," Berlin, 1892.
XX..	Kaufmann	Not cretinoid; C. hyperplastica	Normal	Ziegler's "Beitr.," 1893, xiii., S. 32.
XXI..	Scholz	C. hypoplastica	Vascular struma	"Ueber fötale Rachitis," Inaug.-Diss. Göttingen, 1892.
XXII..	Johannessen ..	C. hyperplastica, not cretinoid	Normal (microscopical examination).	Ziegler's "Beitr.," Bd. 23, 1895.
XXIII..	Salvetti	C. hypoplastica; cretinoid with some signs of myxœdema.	Hypertrophied	Ziegler's "Beitr.," Bd. 16, 1894, S. 29.
XXIV..	Grotthoff	C. malacica	Normal size	"Ueber einen Fall von sogen. fötaler Rachitis," Inaug.-Diss., Berlin, 1895.
XXV..	Bircher	Normal size	Lubarsch u. Ostertag's "Allg. Aetiologie," 1896, S. 51.
XXVI..	Legny and Regnault.	Normal in all	Comptes rend. de Soc. de Biol., 1902, liv., 567.
XXVIII.	Hektoen	Mixed type	Atrophy and fibrosis; hypophysis enlarged; iodine not determinable in thyroid.	Amer. Journ. Med. Sciences, May, 1903.

cretinism, further than to say that it is proved practically beyond doubt that the two are one and the same thing, and due to defect in the function of the thyroid. Any differences are to be explained in respect to the time at which the athyroidia first makes itself manifest. Myxœdema is cretinism manifesting itself in the adult; cretinism is myxœdema of childhood. In opposition to the views of Leblanc and Nasan may be cited the experience of Cestan ("Nouvelle Iconographie de la Salpêtrière," 1901, xiv, 277), who found a condition of chondrodystrophy in a girl nine and a half years old, unimproved by thyroid feeding for nine months, and of Marie (*Presse médicale*, Juillet, 1900, vol. iv.), who in two cases found no benefit from the use of thyroid extract. We should observe, too, that the lesions of chondrodystrophia are said to develop in the earliest period of foetal life before the thyroid is properly formed.

With regard to the anatomical peculiarities of the thyroid in chondrodystrophia it is not always possible to obtain accurate information. So far as I have been able to trace them they will be found in the preceding table.

Unfortunately, not having access to the original papers in all instances, I am not able to give complete information in the above table, and the number of cases might be added to. We see, however, that out of twenty-nine cases the thyroid is abnormal in eight, either absent, atrophied, or hypertrophied. And it is further striking that in all the cases in which the thyroid is obviously diseased, with one exception, the clinical type has been cretinoid; with, in two cases, some additional features resembling myxœdema. The one exception, Hektoen's case, is probably to be explained on the ground of a compensatory action of the hypophysis, which was considerably enlarged, but otherwise of normal structure. In Bowlby's case, which is recorded as a case of cretinism, being observed before the distinctions between the different forms of abnormal osteogenesis were so closely drawn as they are at present, the skin was œdematous and semitranslucent, the nose was broad and flat, and there were no eyelashes or eyebrows. In Salvetti's case the skin was also œdematous. In the one case in which vascular struma is stated to have been present (Scholz), there were apparently no signs of cretinism; but this anatomical condition of the thyroid does not of course imply deficiency of the secretion; rather is it akin to what is found in exophthalmic goitre or hyperthyroidism. This association of defective thyroid secretion, which must be admitted where the thyroid structure is so extremely altered, with the cretinoid type of Kaufmann's chondrodystrophia can hardly be fortuitous, especially when we note that in the cases that are distinctly without cretinoid features, the thyroid has been, so far as we can judge from the imperfect information that we are given, practically normal. In settling this latter point we can admit as conclusive evidence only cases that have been controlled by post-mortem examination. Still, the position is supported to some extent by clinical cases. It is, it must be remarked, difficult to draw conclusions as to the functional efficacy of the thyroid from an estimate of its size alone derived from palpation. Osler (*Trans. Congr. Amer. Phys. and Surg.*, 1897, vol. iv., pp. 190-192) describes two cases of chondrodystrophia in French-Canadian children, who did not present the cretinoid facies, in whom the thyroid was not enlarged on palpation. Joachimsthal (*Deut. med. Woch.*, 1899, S. 288) also reports a case of chondrodystrophia hyperplastica, without the cretinoid appearance, in which also the thyroid was normal on palpation. As corroborative evidence, also, it may be noted that Virchow (*Virch. Archiv*, 1883, xciv., S. 183), in the canton of Glarus, Switzerland, where goitrous cretinism is endemic, found not a few cases of chondrodystrophic dwarfism without the gross signs of cretinism. It would seem, so far as we can judge from so limited a number of observations, that the cretinoid type of chondrodystrophia, as described, is simply a form of cretinism, or at least due to thyroid inadequacy. If this be the case, it then follows that

Kaufmann's chondrodystrophia foetalis is probably not a distinct disease entity, but that several differing conditions are included under the one name. Some stress has been laid on the peculiar retraction of the root of the nose, which is so evident a feature in typical cretinism, as an aid in the diagnosis of these conditions. It should be said that this feature is not always present in undoubted cretinism and, moreover, the explanation given of it, namely, that it is due to premature synostosis of the os tribasilaræ, does not invariably hold good. Some of Kaufmann's cases show that retraction of the root of the nose may be present without premature ossification of the os tribasilaræ. In these exceptions he attributes the appearance to shortening of the bony parts in front of the os. Conversely, the synostosis may take place without producing any effect on the condition of the nose. Consequently too much weight should not be laid on this point.

It would, perhaps, be also premature to conclude that the other forms of chondrodystrophia may not be dependent on thyroid dystrophy. It is true that Cestan, Marie, and Christopher have failed to get benefit from thyroid feeding in chondrodystrophia. As the disease, however, originates during intra-uterine life, by the time the cases come to observation the main damage has been done, and it is not to be expected that any form of medication would have a marked effect on bony structures once they were formed. The only possible chance would be if the cases could be treated from birth; but, so far as I am aware, this has not been done. This fact weakens the therapeutic argument very much. Further, it does not follow that because the thyroid is of normal size and appearance that it is competent to perform its function. While an absolute deficiency in the amount of secretion furnished by the thyroid will undoubtedly produce the symptoms that constitute cretinism or myxœdema, it is quite possible that a relative inadequacy will produce the same symptoms. This aspect of the case, which has been emphasized by Prof. J. G. Adami ("Internal Secretions Considered in their Physiological, Pathological, and Clinical Aspects," *Trans. Congr. Amer. Phys. and Surg.*, vol. iv., 1897) has been constantly overlooked by writers on the subject. The doctrine of internal secretions supposes the existence of some substance, the product of metabolism, for the secretion to act upon. The thyroid, therefore, may be normal, but if the substance upon which it acts is produced in excess, then the gland will be insufficient for its work, and the various symptoms of athyroidia may make their appearance. In some few instances in which the hypophysis has been invaded by a tumor, symptoms of myxœdema have occurred with an intact thyroid, the thyroid and the hypophysis being, as is now well recognized, more or less complementary organs. Relative inadequacy of the thyroid—and, *mutatis mutandis*, the same remark applies to the hypophysis and other glands furnishing an internal secretion—is a factor that can by no means be neglected in these obscure disorders of development. Until, however, we know much more about the nature, chemical and otherwise, of metabolic processes, we must leave such questions to the realm of speculation.

In concluding, we should not forget to say a word or two in regard to the relationship between anomalies in structure and function of the genital tract and the general question of somatic development. It is a matter of common knowledge that the changes in the genital organs which occur at puberty are coincident with an increased nutritional and functional activity of the body as a whole, as is evidenced by the rapid growth, the consolidation of the figure, the production of hair, the deposit of fat, the changes in the voice, and the altered mental characteristics, all of which together constitute the adult type. Certain isolated facts bring this relationship into still greater prominence. Genital hypoplasia, with its associated sexual torpidity, amenorrhœa, and even sterility, has been found in certain dwarfs, in myxœdema and cretinism, in acromegaly, and in some forms of gigantism. This would suggest that there is some

functional relationship between the thyroid gland, the pituitary body, and the genital organs. The almost constant genital insufficiency found in conditions of athyroidia is so well recognized that I need not do more than mention it. That a similar peculiarity may be associated with lesions of the pituitary body is perhaps not so widely known. Some years ago I performed an autopsy on a female about thirty years of age, who died with symptoms of a basal tumor of the brain. The genitalia were markedly infantile in size and appearance. A tumor of the hypophysis was found, although there were no signs of acromegaly. A similar case is one reported by Babin-ski (Society of Neurology, June 7th, 1900), who found signs of infantilism, viz., lack of body hair, amenorrhœa, an excess of fat, in a girl of seventeen, but without acromegaly, who post mortem exhibited a tumor of the pituitary. Analogous peculiarities have been found in the male in such cases. While it is true that children the subjects of atrophy of the genitals are often small, instances of the reverse are not unknown. Eunuchs are often of more than normal height. The increase in length is most manifest in the lower limbs, a peculiarity that is to be observed also in the capon, or castrated chicken, and in the ox. The relationships suggested by the above observations might be depicted graphically in the diagram (Fig. 5138).

It is in view of these facts that Freund, Klebs, and Verstraeten, have advanced the theory that anomalous evolution of the genital function is at the bottom of developmental dystrophy. If genital evolution be in excess, gigantism or acromegaly will occur; if defective, infantilism or dwarfism results. It seems to me, however, that this is much too strong an assertion, and one that is not supported by the facts, as we know them. Such a theory supposes the existence of an internal secretion in the case of the genital organs, to wit, the testes and ovaries, the evidence for which is not beyond question. Further, the association between genital anomalies and developmental peculiarities is not necessarily direct, as cause and effect, but may be indirect through some third factor. We have experimental evidence to show that defect of the thyroid will produce hypoplasia of the genitalia, but not the converse, and in this case as a matter of fact genital hypoplasia is simply part and parcel of a systemic developmental defect. In the case of the pituitary evidence is scanty, inasmuch as experimentation, except in the single particular of pituitary feeding, is extremely difficult. The evidence, so far as I can gather it from autopsies, seems to favor the view that certain lesions of the pituitary, provided they arise early enough, may prevent the proper development of the genital organs. There is absolutely no evidence to prove that hypoplasia or any other pathological condition of the genitalia has produced disease of the pituitary. Could it do so, one would suppose that, considering the very respectable number of cases of aplasia and hypoplasia of the genital organs that have been described, some abnor-

mality of the pituitary body would occasionally have been noted. This is, however, not the case. It would seem more probable that genital hypoplasia, if not indeed always an effect, is an associated condition merely. In regard to the factors at work in this very interesting but obscure condition of anomalous development, the sum and substance of the whole matter is that our views cannot attain finality until we know much more of the chemistry of the internal secretions and of metabolic processes generally. Hitherto the anatomical peculiarities and the pathological chemistry of the thyroid and pituitary glands in cases of dwarfism and giantism have not been sufficiently studied. Nevertheless, I think that after due consideration of the facts brought out in our study of dwarfism, we may be able to draw certain conclusions with a fair degree of probability.

1. That there are two main types of dwarfism, *essential dwarfism* and *symptomatic dwarfism*, which etiologically belong to two distinct categories.

2. The former are to be attributed to peculiarities inherent in the germ cells or acquired shortly after segmentation of the fertilized ovum, the exact nature of which at present remains obscure, or to acquired intra-uterine disturbances. The latter are due, not only to the causes just mentioned, but also to acquired disease. In true dwarfism the defect of development is in time and extent; in symptomatic dwarfism the manner of growth is perverted as well.

3. There is a close association between such conditions as "fœtal rickets," cretinism, osteopathrosis, osteoporosis, osteogenesis imperfecta.

4. Fœtal rickets so

called has nothing to do with rickets as it is ordinarily understood.

5. The term *chondrodystrophia fœtalis* is a misnomer, inasmuch as it implies a local lesion, and, moreover, attributes it to a nutritive cause, whereas not only the cartilage but the bone and soft tissues are involved. Virchow is probably correct in regarding it rather as a developmental anomaly.

6. The three types, *chondrodystrophia hyperplastica*, *chondrodystrophia hypoplastica*, and *chondrodystrophia malacica*, are probably not varieties of the same disease.

7. *Chondrodystrophia* of Kaufmann's first or cretinoid type is probably a modified cretinism.

Albert George Nicholls.

EMBALMING.—This article is intended to furnish useful information to the medical practitioner who may be called upon to preserve a dead body for a limited period of time. This duty can occur only when it is not possible to secure the services of the professional embalmer.

When the object in view is simply to keep the dead human body from undergoing decomposition for a few days, there are a number of methods from which the physician may make a choice. Thus, for example, when it is possible to obtain ice in plenty and the services of a person who can be trusted to renew the supply as fre-

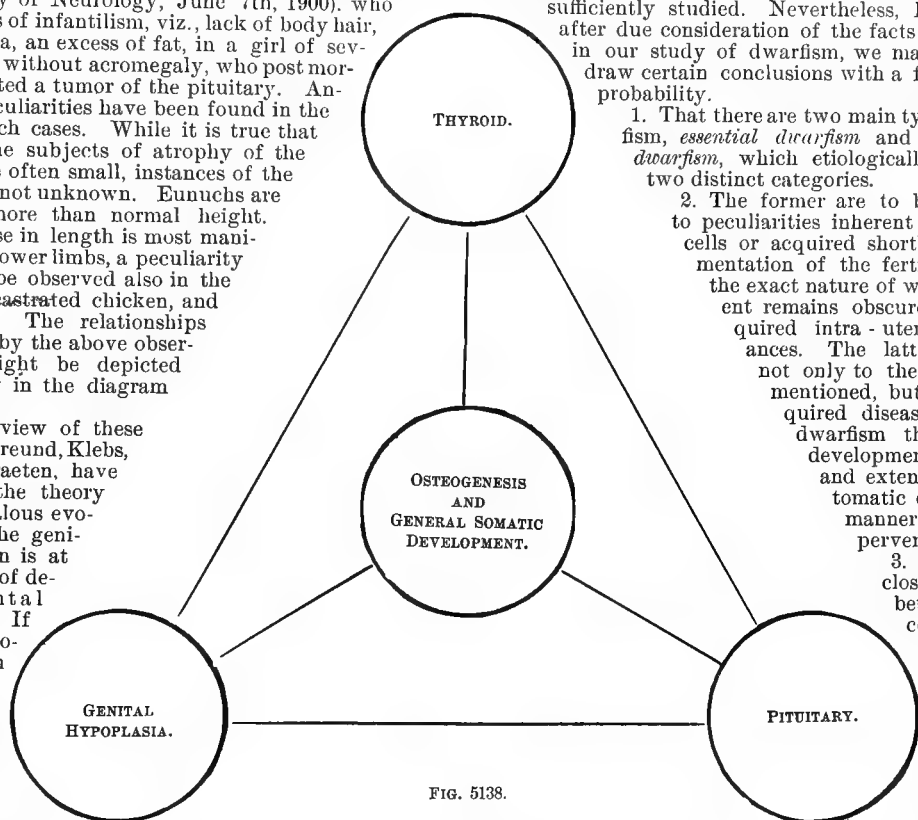


Fig. 5138.

quently as may seem desirable, this method of preventing or at least postponing decomposition is probably as good as any other that can be suggested. But it is often impossible to obtain ice in the desired quantity, or the period of time during which the dead body must be preserved is longer than is compatible with the employment of this method. Under these circumstances it becomes necessary to fall back upon some other procedure, one, for example, which depends for its efficacy upon the employment of chemical reagents. Among the large number of such procedures the physician may be compelled, by reason of the circumstances in which he happens to be placed, to select one of the simpler and less efficacious methods. I will therefore mention a few of these first, reserving to the last an account of the steps which one must take if it be desired to preserve the dead body in good condition for a reasonably long period of time—for months or even years. It is only to such a procedure that the term embalming may with propriety be applied.

Methods Suited to the Preservation of a Dead Body for a Short Period of Time.—(a) Place the body, without opening it, and as soon as possible after death, in sawdust mixed with powdered zinc sulphate. The skin, it must be remembered, has a tendency, under continued exposure to this reagent, to assume a yellow color.

(b) Open and clean the body and viscera, and keep all the parts that can be reached saturated with a corrosive sublimate solution (1 in 1,000) or a formalin mixture (of a strength of from five to ten per cent.). Cloths saturated with the same fluid should be wrapped around the body, and enough of the preservative should be added from time to time to keep the cloths constantly moist.

(c) Open a femoral artery at the apex of Scarpa's triangle and inject a solution of arsenous acid (eight drachms in 9 kgm. of alcohol; cinnabar, q. s.). Then open the abdominal cavity, wash out the cavities of the stomach, bladder, and intestines, and inject the preservative solution into them freely.

(d) Camphor dissolved in alcohol, in the proportion of 1 part of the former to 6 of the latter, can be used effectively as a preservative fluid. Another mixture is the following: Oil of turpentine, 5 pints; Venice turpentine, 1 pint; oil of lavender, 2 ounces; oil of rosemary, 2 ounces; vermillion, q. s.

Another mixture, which has been used with some measure of success in England, is the following:—To one pint and a half of glycerin add three quarters of a pound of white arsenic (arsenous acid) and boil; afterward add one gallon of pure glycerin. Still another useful mixture is one composed of alcohol and glycerin in equal parts (each representing forty-seven and a half per cent. of the entire bulk), and carbolic acid to the extent of five per cent. A small quantity of arsenic (about one per cent.) may, if desired, be added to the mixture.

All of the ingredients mentioned in the preceding paragraphs are, as a rule, easily obtainable, and the manipulations required call for no special skill. At the same time it must be remembered that these procedures can at best retard decomposition for only a relatively short time. Thoroughly satisfactory results can be obtained only through the more elaborate and painstaking methods adopted by the professional embalmer.

An Effective Method of Embalming.—Mr. Frank E. Campbell, of 241 West Twenty-third Street, New York City, a recognized authority in embalming, has very kindly allowed the use of the following description of the method of embalming which he prefers:

"I. Bathe and dress (in underclothing) the body to be embalmed, and place it upon a board supported in an inclined position. Close the mouth and eyes, and securely plug all orifices.

"II. Place within easy reach all the instruments and various objects that will be needed, viz., scalpel, aneurism needle, blunt hook, scissors, arterial tube, five six-inch lengths of linen thread for tying about the vein and artery when raised, a threaded needle suitable for sewing up incisions, a bulb syringe, a large bottle filled with the

embalming fluid, a sponge, a supply of cotton, etc. Sink the suction end of the tubing of the bulb syringe into the embalming fluid contained in the bottle and squeeze the bulb several times in order both to fill it with the fluid and to force out the air which it contains. When these objects have been accomplished the discharge end of the syringe should also be introduced into the bottle, in order that no leaking may take place.

"III. Connect the aspirating pump, by means of tubing and a gooseneck, with an empty aspirating bottle suitable for holding the blood to be withdrawn from the body. Then attach to the free end of the tubing a long silk-covered vein tube, or, better still, a flexible wire catheter.

"IV. Expose the femoral vessels in Scarpa's triangle over an area two or three inches in length and dissect them clean. Then, with one of the lengths of thread already prepared, tie the artery at the lowest possible point with a firm knot, for the injection is to be made only in an upward direction.

"V. Next, pick up the vein and treat it in the same manner as the artery, remembering, however, that the structure of the vein is fragile and that it may easily be punctured or torn. Make a slit, about a quarter of an inch long, lengthwise in the vein. As blood will escape from the vessel when it is thus opened, it is well to prevent this by making pressure upon the vein with the finger or with a blunt hook. Insert the vein tube into the opening in the vein and push it upward to or near the right auricle of the heart. Pass a piece of the thread snugly, but not too tightly, around both vein and tube, and tie it with a simple knot. Attach the tubing of the aspirating pump and begin to pump the air from the bottle. When the air has been withdrawn from the bottle, the vacuum will draw the blood from the body by way of the vein tube. If no blood flows into the bottle after the air is pumped out, it may be assumed that a clot of blood has probably entered the free end of the tube in the vein, or else that there was no blood at the point where the end of the tube rested. Draw the tube slowly downward, and, if there is still no flow of blood, push the tube as far back into the vein as it will go, detach the rubber tubing from it, and, by means of the bulb syringe, inject a bulbful of aqua ammoniæ, for the purpose of dissolving the clotted blood. After this has been done, resume the operation of aspirating. When all the blood that can possibly be removed in this manner has been aspirated, withdraw the tube for about one-third its length, and let it remain in the vein. (Always keep a vacuum in the bottle.)

"VI. Next, pick up the artery, slit it, and insert the arterial tube with care. Then pass the remaining piece of thread around it as far up as you can, and tie it with a simple knot. Attach the bulb syringe (previously made ready) to the tube and begin the injection slowly. When about one-third of a quart of the preservative fluid has been injected, stop and begin once more to aspirate the vein, for by this time the fluid injected into the artery is forcing the blood ahead of it, and the blood will flow again more freely.

"VII. Administer the injections and the aspirations in alternation until a quantity of the preservative fluid varying from three pints to five or six pints, according to the size of the body, shall have been injected, and also until a clear fluid, and not a bloody one, escapes from the vein tube as a result of the aspiration. Any discolorations of the face, ears, or neck, will probably by this time have disappeared. If it should be found, however, that a slight discoloration still remains in the lower part of the ears, or in the neck, a slight rubbing will in most cases remove it.

"VIII. After it is seen that only clear fluid flows into the blood bottle, draw out the vein tube and tie the vein tightly.

"IX. Continue the injection of fluid into the artery until the veins of the temple, the large vein on the forehead, and the jugular vein, as well as the veins in the arms and hands, indicate that they are filled. Then re-

move the arterial tube and tie the artery tightly with the same thread that held the tube in place. Pack the wound well with moist 'lintine,' and sew up the incision with the 'baseball' stitch, drawing the edges snugly together.

"The arterial work is now completed.

"X. For successful work on the cavities of the body there will be needed a twelve-inch trocar, an instrument that will reach every point where it is desirable to apply the preservative fluid. At the same time it must be remembered that much damage can be done with a trocar of these proportions if it be not used with care. It is therefore important to avoid injuring the trunks of arteries and veins, and the various organs.

"Insert the trocar just far enough to penetrate the abdominal wall, and connect it with the aspirating pump. Draw the gases and liquids through it into the empty bottles. Through his knowledge of the anatomical relations of the different organs the physician should be able, without removing the trocar from the opening in the abdominal wall, to carry out successfully the following procedures: He should puncture the stomach and draw from it all the gases and liquid contents, and then, after he has accomplished this, and without removing the trocar, he should inject two bulbfuls of the embalming fluid into the cavity of this organ. The aspirator should then be re-attached to the trocar and the latter should be made to pierce the intestines, both the large and the small. In this way it will be possible to remove any gases or fluids which these organs may contain. The bladder should be treated in the same manner. Never puncture the liver, as it cannot be aspirated or injected, and the original arterial injection may be trusted to preserve it from decomposition. As a final step connect the trocar with the syringe and copiously flood the intestines with the preservative fluid.

"Where death occurs from pulmonary tuberculosis or from pneumonia, turn the point of the trocar upward toward the lungs and cause it to penetrate into the thoracic cavity as far as it will reach. Aspirate first from one pleural cavity—for example, the right—and then from the other; care being taken, after the aspiration of the first pleural cavity, to withdraw the trocar well into the abdominal cavity before the attempt is made to push it on into the second. When both pleural cavities have been thoroughly aspirated, flood each of them with embalming fluid in a cautious manner and then withdraw the trocar altogether.

"With needle and thread close the opening in the abdomen by means of a drawstring suture. Pack the nose with lintine thoroughly moistened with embalming fluid, and pack the rectum and vagina in the same manner. The embalming will then be completed."

While Mr. Campbell does not state which particular preservative mixture he considers the best, it is fair to assume that sufficiently good results may be obtained by the employment of any one of the half-dozen or more standard embalming fluids which are offered for sale in the shops.

William Sohler Bryant.

EMPHYSEMA, SUBCUTANEOUS.—By this term, or pneumatosis, is meant the presence of air or other gaseous compounds beneath the skin.

The resultant symptoms are these: a swelling covered with skin of either normal appearance or, if the pressure upon it be great, rather pale; this tumor pits upon pressure, as in the case of anasarca, but the pitting more quickly disappears when the swelling is due to the presence of air. Palpation causes a peculiar crackling or crepitation in the subcutaneous tissues. If the air have entered from without, a wound or puncture can generally be discovered; if from within, expiratory efforts with closed lips and nostrils will generally produce immediate increase in size. It is possible for the whole subcutaneous tissue to become inflated from any superficial part of the body as a starting-point.

In case the emphysema is that of decomposition, there may be an altered hue of the integument; but the dis-

coloration, of course, is entirely independent of the emphysema.

Subcutaneous emphysema may result from causes either traumatic or pathological. Among instances of the latter may be mentioned ulcers or abscesses communicating with the air passages, and, as already suggested, gangrene.

We may include in the discussion of this subject emphysema of other parts external to the lungs, such as mediastinal and submucous collections of air.

In the head, orbital emphysema sometimes follows a blow of sufficient violence to break one of the thin and fragile bones of the inner wall of the orbit—the lachrymal or the orbital plate of the ethmoid. If, soon thereafter, the patient blows his nose, the compressed air finds a ready exit from the nose into the orbit, and distends the lids.

Eustachian emphysema: here an ulcer of the tube, or a rupture following awkward Eustachian catheterization, has led to distention and approximation of the pharyngeal walls by the dissecting air. Blowing the nose and the Valsalvan experiment increase the emphysema in these cases. Von Tröltsch¹ mentions a case, within his own experience, in which dysphagia consequent upon such emphysema persisted for five days.

In the neck we may have escape of air as a result of foreign bodies, ulcers, or abscesses perforating the œsophageal, laryngeal, or tracheal wall; but emphysema will not be produced if, as a result of the perforation, a broncho-œsophageal fistula be established.

Ulcers of the larynx or trachea may lead to submucous dissection by air. Wounds of the neck penetrating these parts may be followed by subcutaneous emphysema if there is not free escape for the expired air. Under these circumstances inflation of the skin has been known to occur over an area extending from the head to the scrotum.²

As a rule, the consequences are not serious; but Holmes³ quotes Hilton as stating that emphysema about the phrenic nerves may so interfere with their functional integrity as to cause death.

During tracheotomy, and afterward if much inspiratory difficulty be present, Champneys⁴ finds that anterior mediastinal emphysema, and even pneumothorax, are liable to occur; and this is especially so if artificial respiration by Schultze's method be employed.

In the chest we may have the surgical symptom in question produced in several ways. Pathologically, as by the opening of a vomica or abscess of the lung into the parietes of the chest, the two pleural surfaces being adherent at the point where the abscess perforates. (If the parts were not adherent at this point, there would, of course, simply be a pneumo- or a pyopneumothorax.) Emphysema sometimes complicates wounds of the chest-wall, both the penetrating and the non-penetrating varieties. In the latter instance, the air which enters the wound from without during one movement of respiration is prevented in a valvular way from escaping during the opposed movement, and is disseminated by the muscular and tegumentary pressure upon it during this movement. In the case of wounds penetrating the parietal pleura only, we may, besides the consequent pneumothorax, have a subcutaneous emphysema from the same reason.

Wounds that penetrate the lung, and a puncture of the lung by a fractured rib, are alike liable to produce emphysema, air escaping from the lung with the same result as in the case last given.

An additional and rare variety of traumatic emphysema of thoracic origin is that consequent upon rupture of air cells by violent expiratory efforts, with a closed or partially closed glottis, as while coughing, straining, or blowing a wind instrument. Here the air makes its way between the lobules, and, unless it ruptures the pleura, producing pneumothorax, it escapes at the root of the lung into the mediastina, and thence into the cellular tissue of the neck, becoming subcutaneous.

Guttman⁵ says: "Most of the cases of this variety of emphysema are observed in connection with croup, diph-

theritis of the larynx, whooping-cough, and bronchitis in children, and with advanced pulmonary emphysema in the aged."

In 1884 I met with the only case which, as yet, I have found complicating whooping-cough. The patient, a child of two years, had been suffering for about three weeks, the parents said, from violent fits of coughing. I was called to treat the sudden appearance of "dropsy" in the case. I found the skin of the head, neck, and chest distended, crepitation everywhere well marked, and no dropsy. Whenever the child coughed the swelling increased in size suddenly, apparently causing distention first in the left supraclavicular region. The respiration was rapid, but seemingly free; the pulse rapid and feeble. The child died within a few hours. Unfortunately, no autopsy was allowed.

In the *abdomen* we may have subcutaneous emphysema from ulcerative perforation of the stomach or intestine at a point previously adherent to the abdominal wall. Unless such adhesions prevent it, gas will escape from the viscera into the peritoneal cavity.

TREATMENT.—As a rule, air beneath the skin is of slight consequence and requires no treatment, becoming absorbed after a time. If, however, important parts—as the phrenic nerves, or the larynx, trachea, etc.—are subjected to a degree of pressure injurious to respiration, or if the subcutaneous air is spreading further and further, we may employ pressure at the point of escape, or may make incisions through the skin to give relief to tension, or both.

Subcutaneous emphysema possesses an interest for us outside of its pathological or accidental causation. It has often been induced intentionally by the malingerer; and, moreover, its production has been seriously advocated by Dr. H. R. Sylvester⁶ in an article entitled "On Life-saving from Drowning, by Self-inflation." Here it is recommended that those in peril of the deep shall make a small puncture or cut in the cheek, leading from the mucous membrane about opposite the first molar to—but not through—the superficial fascia and skin; and then, closing the lips tightly, they shall proceed to blow themselves up, until the skin of the head, neck, and chest is distended. Dr. Sylvester alleges that a moderate and quite painless and harmless inflation is ample to keep one afloat without effort.

It seems probable that Vidocq refers to such a practice when, in his memoirs—as mentioned by Gavin,⁷—he asserts that he could make his head swell like a bushel, without giving pain, and that he could remove all traces of it by the day following.

In order to test the degree of pain, and the subjective effects of such distention upon the skin, I some time ago performed the following experiment, assisted by my friend Dr. F. A. Manning: Having connected, by a piece of rubber tubing, a hypodermic needle with my compressed-air receiver, I forced air beneath the skin of my left forearm until the limb was much increased in size, the skin tense, and emphysematous crepitation could be felt from wrist to armpit. The pain was very trifling in amount. The distended skin was somewhat anæsthetic; whereas before the injection I could distinguish separate points on the anterior surface at an average distance of 4 mm., immediately thereafter I could name them only when they were 10–15 mm. apart. Still, pinching and pricking were distinctly painful. The emphysema thus induced was slow in disappearing. It was still somewhat noticeable on the third day after the experiment.

As regards the production of emphysema upon the human subject with intent to deceive, it has been employed to simulate hernia, hydrocele, hydrocephalus, ascites, etc. Gavin (*op. cit.*, p. 389) says, "It is a trick used every day by butchers, and has been known from time immemorial by the Ethiopians and mendicants of Abyssinia." Beck⁸ quotes Sauvage's "Nosology" regarding a mendicant who "gave his child all the appearances of hydrocephalus by blowing air under the tegument of the head near the vertex." He also cites a case of emphy-

sema of the abdominal parietes, induced by a woman who wished to feign dropsy.

Sir George Ballingall⁹ declares that the artificial production of this for the simulation of other diseases is regulated by a recipe current in the British army.

The differential diagnosis of the tumors so caused presents no difficulty.
Robert H. M. Dawbarn.

- ¹ Treatise on the Diseases of the Ear.
- ² Plaies du larynx, de la trachée, etc., par le Dr. Paul Heurteloup, Paris, pp. 53–77.
- ³ Surgery, vol. ii.
- ⁴ Med. Chir. Transactions, 1882, p. 75 *et seq.*
- ⁵ Handbook of Physical Diagnosis, p. 27.
- ⁶ London Lancet, January 3d, 1885, and August 29th, 1895.
- ⁷ Gavin on Feigned Diseases.
- ⁸ Medical Jurisprudence, vol. i., p. 74.
- ⁹ Military Surgery, p. 584.

ENTEROPTOSIS.—(Synonyms: Glénard's Disease, Splachnoptosis [Stiller].)

INTRODUCTORY AND HISTORICAL.—Anomalous downward displacements of the abdominal viscera were described by Virchow, Leube, and others, several years before Glénard's monograph appeared. In this article, which was published in 1885, Glénard set forth his views upon enteroptosis and connected therewith certain nervous phenomena which have since borne the name of "Glénard's disease." Prominent among the features of this symptom complex, which Treves is pleased to call "that medley of symptoms," are downward displacement of the stomach, a movable right kidney, various digestive disturbances, and often very typical neurasthenic symptoms.

The interest thus awakened in postural anomalies of abdominal organs by Glénard's article is as keen to-day as it was eighteen years ago, and many physicians have verified the statement of that author which he made with such enthusiastic earnestness at the close of his early monograph. "I can affirm," wrote Glénard, "that the physician who will follow my directions and strive to verify my statements in such cases will find in his practice the satisfaction which a positive diagnosis gives to both physician and patient, from which alone a proper prognosis can be made, and that satisfaction, the greatest of all, which directs the treatment and avoids for the patient the trial upon him of so many remedies, while at the same time it secures him relief and prevents the physician himself from falling into therapeutic scepticism."

The investigations made by the French were rapidly followed by similar work among the German clinicians, with the result that another view of the cause of the displacements was advanced. Then the English and American writers contributed articles and case reports upon the subject, dealing with the nature and anatomy as well as with the etiology and treatment of the disease. One cannot close this introductory historic note without mentioning the fact that the lectures of Arthur Keith on the nature and anatomy of Glénard's disease comprise one of the best studies upon this phase of the question yet published and will be duly recognized later in this article.

The application of the term Enteroptosis.—It would appear that Glénard's original article included a description of a displacement of the intestines alone. The Germans broadened the application of the term and made it to include, in most instances at least, ptosis of all the abdominal viscera. Scherwdt, however, pleaded that the term was applicable when at least two of these organs suffered downward dislocation. If, on the other hand, one would wish to be specific, the organs so displaced might be specified by *gastroptosis*, for instance, or *nephroptosis*, and so on.

ETIOLOGY.—The study of visceral ptosis, from the etiologic standpoint, has provoked a variety of theories differing so widely that it is manifestly impossible to find one theory broad enough to explain all cases. It has been urged that enteroptosis is a congenital anomaly (Stiller); that it is a constitutional ailment (Scherwdt), a general atony of nervous system and muscles; that it is the result of wearing corsets, or tight waistbands with heavy skirts (Meinert); that it is a result of a neurasthenia basis (Charcot); that rapid emaciation or a severe illness

may account for it; that to overlifting or frequent pregnancies many cases may be traced; that adhesions, the result of peritoneal inflammation, may pull down one organ after another (Trevcs); that it is a reversion to a fetal or an embryonic type (Rosengart); and the latest, and by no means the least ably supported theory, is that which would regard enteroptosis as "a result of a vitiated method of respiration," and assign it to a place among respiratory diseases (Arthur Keith).

It is admitted, we believe, that there are several factors which maintain the various abdominal organs in position, and of these the most important are: (1) The intra-abdominal pressure, and (2) the ligamentous attachments of the viscera to the body walls. These two are so important that when either fails ptosis may result. Hence it may be said that these factors are those by which the normal postural relations of the viscera are maintained. It is not difficult then to believe that any cause, or number of causes, which lowers the intra-abdominal pressure by exhausting the muscular tone, or which weakens or stretches the supporting ligaments, would readily alter the relation of the organs—especially of the heaviest organs or of those with weakest supports—and result in ptosis.

Thus, as one reviews the various etiologic factors suggested above, one finds most of them—perchance all of them—applicable to a large number of cases. The last theory suggested, however, "enteroptosis as a result of a vitiated method of respiration," certainly requires some explanation. When Dr. A. Keith remarks that enteroptosis is a result of a vitiated method of respiration, he means, doubtless, that faulty movements of the diaphragm, resulting from a variety of causes, determine visceral ptosis, and that whereas under normal relations of the muscles of inspiration—the diaphragm, the external intercostals, and the interchondrals—to the muscles of expiration, and chiefly those of the abdominal walls, there is but slight downward displacement of the viscera. The organs swing and move upon each other, often as much forward as downward, maintaining their normal positions and postural relations. As a result of various conditions the inspiration muscles may "gain the upper hand and the muscles of expiration yield," and ptosis is induced. This writer strongly emphasizes the importance of the diaphragm in bringing about the changes incident to enteroptosis. He remarks that the inspiratory downward displacement, if once the diaphragmatic supports commence to yield, is one of the factors in the causation of visceral ptosis; and while minimizing the function of visceral bonds in the causation or prevention of enteroptosis, he maintains that the active contraction of the crura is the most important factor in the production of visceral ptosis, acknowledging in the same article that while the supports of the diaphragm are threefold—abdominal, costal, and thoracic—doubtless that derived from the abdominal muscles, the muscles of expiration, is of the most importance.

At all events, one is justified in ascribing highest importance to the action of these muscles, since it appears that the normal respiratory swing of the organs, the stomach, liver, and spleen, gives place to downward displacement in the presence of relaxation of the abdominal support, or what is even worse, perhaps, when the body cavity is constricted by corsets or distorted by disease, the action of the diaphragm pushes the organs down. Corsets when applied prevent an inspiratory downward displacement of the liver, but when removed the relaxed condition of the muscles—being too weak to oppose the dropping—favors ptosis.

"The condition essential to the displacement of either kidney is a diminution of the subdiaphragmatic space which may be accounted for, (1) by compression of the thorax with clothing, (2) by a partial collapse of the thoracic walls, following chest or spinal disease, and (3) by the permanent contraction of the diaphragm, which follows a relaxed or parietic condition of the abdominal walls." The left kidney is not displaced so frequently as the right, from the fact that "the left hypochondrium

is provided with a safety valve in the shape of the splenic flexure of the colon." So that when the subdiaphragmatic space is lessened, the "colon is extruded and the other organs are left undisturbed." Again, the close attachments of kidney to spleen, and of spleen to diaphragm, prevent dislocation. From the domain of comparative anatomy one may gather some clew also to this condition. It is affirmed that with the evolution of the orthograde posture and the orthograde type of respiration, mesenteric adhesions, which appeared one after the other in five different areas, spread out and bound the alimentary tract more and more to the abdominal wall as the animal became more and more orthograde in posture. Hence, various degrees of extent and strength of mesenteric adhesions due to arrest of development or otherwise, may help to account for visceral ptosis, in some instances at least.

Whatever the active causes may be which bring about enteroptosis, it may be said that the intra-abdominal pressure is lowered, the organs may be pulled down, and there is more than a mere probability that a congenital predisposition exists in the character of the supporting tissues of the organs, whether these be ligaments or muscles, or both.

CLINICAL FEATURES.

SYMPTOMS.—Enteroptosis does not invariably give rise to symptoms, or, in other words, a considerable degree of downward displacement of one or more of the abdominal organs may exist without calling forth any complaints. On the other hand, however, whether as a result or not cannot always be established, one finds a variety of symptoms referable to the digestive tract, the nervous system, the condition of the blood, and so on; in a word, all manner of subjective symptoms may exist, from the severest abdominal pain, usually spasmodic, to the mildest paræsthesia.

It must be admitted, however, that, prominent and more frequent among the complaints urged by the subjects of enteroptosis, are those of digestive disturbances—distressful weight after food, referred to the right upper quadrant; sometimes spasmodic pain; sometimes vom-

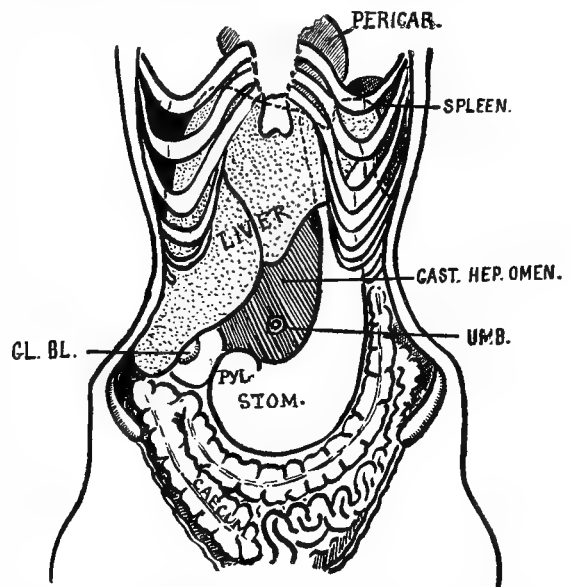


FIG. 5139.—Partial Ptosis of the Viscera in a Woman Aged Forty-five Years. The duodenum descended as far as the brim of the pelvis. (Keith.)

iting, flatulence, constipation, and throbbing in the abdomen. The distress, which in pronounced cases is for the most part constant and referred to the upper quad-

rants, is promptly relieved on assuming the horizontal position, only to return again on getting up and walking about. Hence some persons make this complaint prom-

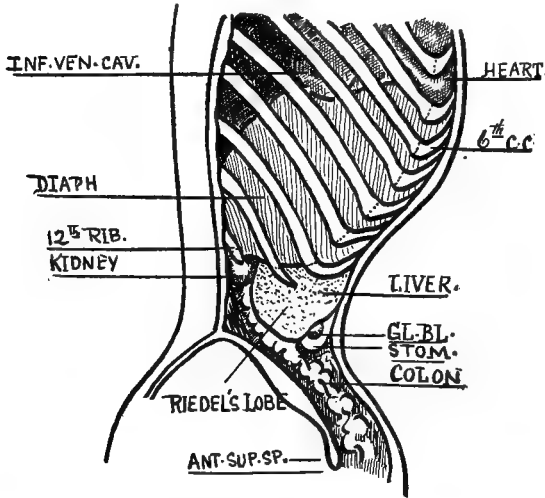


FIG. 5140.—Lateral View of the Same Subject. (Keith.)

inent while speaking of their symptoms. It is interesting, in this connection, to note that constipation, which in one case under the writer's observation was very obstinate, at different periods always disappeared when the patient lay in bed for a few days.

It has been seen that the subjects of enteroptosis are mostly women. Those in whom the condition is marked

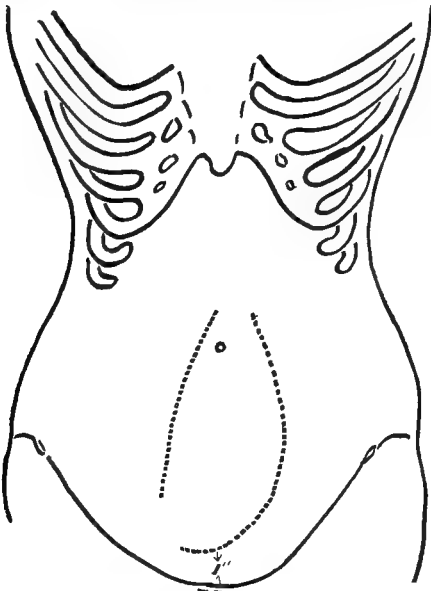


FIG. 5141.—Stomach Vertically Situated and Prolapsed. Located by illumination.

are usually tall and thin, with no compactness of form, while the facial expression in many instances bespeaks a "neurasthenia basis," and, according to Keith and Williams, in cases of visceral ptosis, there is commonly a marked forward curvature of the cervical region of the spine—"ewe-neck."

The examination of the abdomen should be made in both the upright and dorsal positions. In the former attitude one finds, in typical cases, the lower part

of the abdomen flaccid and prominent, overhanging the symphysis pubis—the "Hängebauch" of the Germans (Fig. 5140), contrasting strongly with the upper quadrants which are usually flat or hollowed out. Meinert holds that such a pendulous abdomen holds a dilated stomach and not a dislocated one. It is in the dorsal position, however, that one gets positive evidence of the postural anomalies of enteroptosis. The epigas-

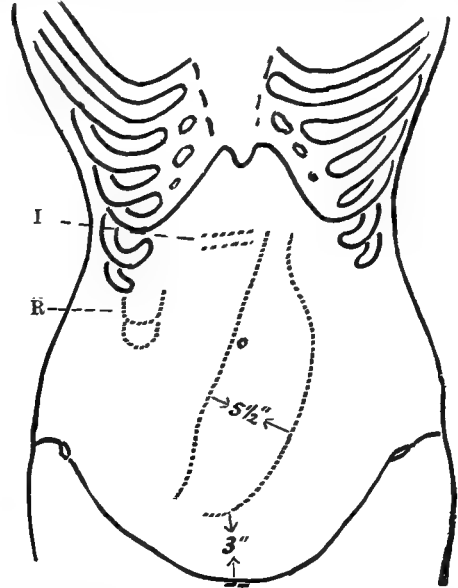


FIG. 5142.—Stomach Vertical or Nearly So. Located by illumination. The "corde colique transverse" is well shown. Right kidney (R) is prolapsed.

trium is usually flat and somewhat scaphoid, with wide-spread pulsations, while the peri-umbilical region is prominent. Peristaltic waves may be seen crossing the

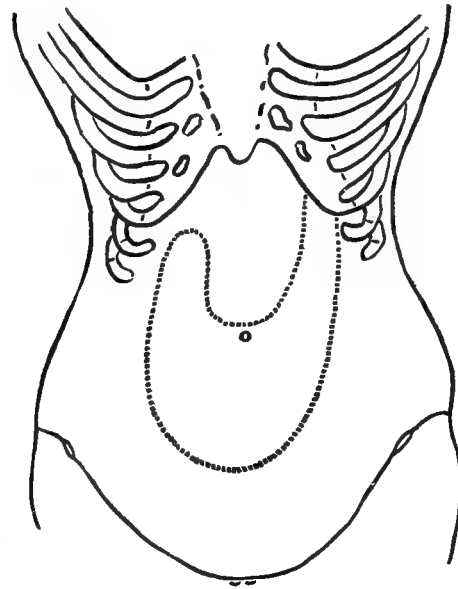


FIG. 5143.—Showing Tendency to V-shape of Stomach on Inflation.

abdomen from side to side; the recti abdominales are frequently widely separated, as may be shown either by palpation or by directing the patient to lift the head and

oulders unaided by the hands or elbows, when a prominent central ridge appears running from the ensiform cartilage downward. The usual methods for determin-

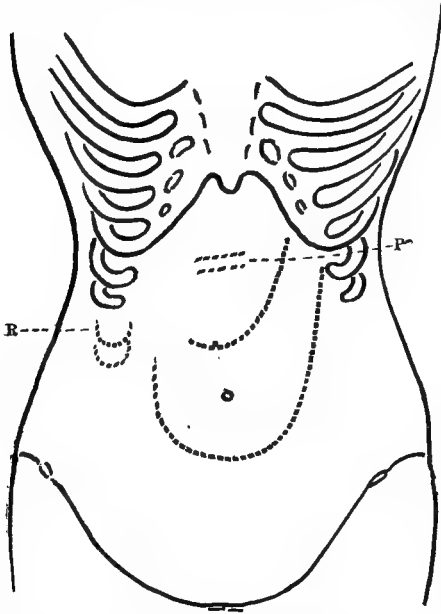


FIG. 5144.—Showing Gastropotosis and Nephropotosis. P, The “corde colique transverse.” (Pancreas is well shown.)

ing the positions of the different organs should be resorted to: palpation and percussion for the solid organs, while inflation and illumination, as well as auscultatory percussion, may determine the situation of the stomach,

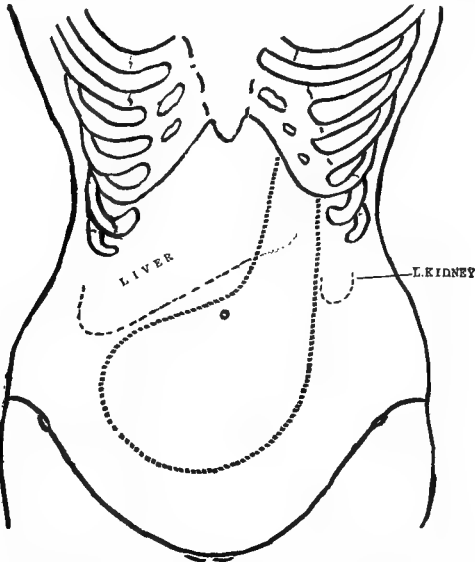


FIG. 5145.—Showing Ptosis and Dilatation of Stomach. Ptosis of the liver and of the left kidney.

tc. Of these methods there seems but little doubt that inflation is the most accurate. It is important of course to distinguish between a displaced stomach and a dilated stomach. Indeed, when that organ is displaced it is usually dilated to some extent.

The organs usually found prolapsed, in cases of enterptosis, are the stomach, the right kidney (movable or oating), and the colon (Fig. 5139). There is, however,

increasing evidence to show that the liver is much more frequently dislocated than was at one time supposed. The left kidney and the spleen are implicated in this condition rarely as compared with the right kidney. The pancreas may be displaced also, chiefly at its head. Not infrequently the pelvic organs suffer the same displacement. The diaphragm and heart may participate in a general ptosis.

With reference to the determination of the position of the stomach, it is important to remember that normally the lesser curvature does not come into view when the organ is inflated, and that the whole of the organ lies above the umbilicus. Hence, when the lesser curvature is seen, and its normal relation to the greater curvature (four to four and one-half inches) is not greatly altered, gastropotosis is present, and in proportion as the lesser curvature approaches the umbilicus, or goes even below it, an increasing degree of gastric dislocation obtains. The stomach is sometimes seen in the oblique or almost vertical position (Figs. 5141 and 5142), and not infrequently the pyloric end is dilated, forming a three-quar-

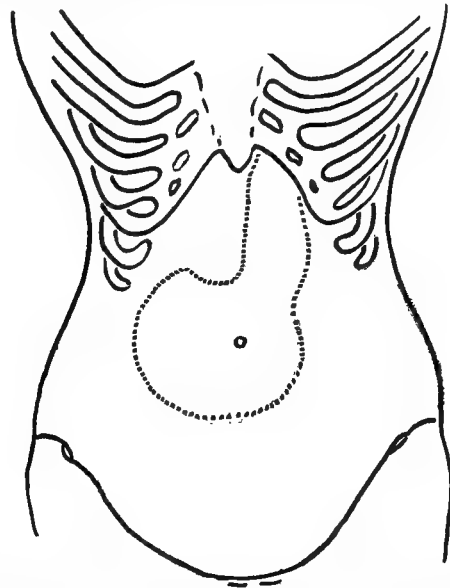


FIG. 5146.—From a Man with Kidney Freely Movable and Characteristic Symptoms.

ter circle with the umbilicus as centre when outlined upon the abdomen. Again, the stomach may be somewhat V-shaped (Figs. 5143 and 5144).

What is the small band which is palpable running across the abdomen about two inches or so above the umbilicus? (Figs. 5142, I and 5144, P.) Glénard termed it “la corde colique transverse,” and regarded it as the “colon transversum.” There is good reason to doubt the correctness of this view. If the stomach is low the colon is generally lower, and in a case in which the band was most typically found by the writer, operation proved it to be the pancreas. In palpation of the abdomen Glénard laid special stress upon a test of considerable diagnostic value. The examiner, standing behind the patient, who is also in the erect position, places both hands flatly over the lower zone of the abdomen and applies firm and gentle pressure upward and backward. In the great majority of cases of enterptosis this act affords considerable relief to the distressing dragging sensation felt in the epigastrium and abdomen. At the same time the result when “l’épreuve de sangle” is applied, is an index to the treatment. (I am greatly indebted to my house physician, Dr. J. R. Byers, for the accompanying illustrations.)

Stiller's Sign. (Costa fluctuans decima.)—Stiller re-

gards enteroptosis as of a neurasthenic origin, and looks upon the presence of a floating tenth rib as indicative of the presence of a neurasthenic tendency. Observations upon this point reported by Meinert, Zweig, Arneill, and others, go to show that this sign in the diagnosis of enteroptosis, or neurasthenia, is scarcely so important as Stiller would have it.

With respect to the relation of enteroptosis, more especially gastropotosis, to chlorosis, it must be said that it is not that of cause and effect—no characteristic blood condition is found in cases of enteroptosis, and many cases of chlorosis occur in which there is no evidence of visceral displacements.

Jaundice, which has been seen in several cases, may result from a variety of causes. "Gall stones are commonly, if not always present, in cases of enteroptosis." This statement, made by Dr. A. Keith, seems rather too broad, although it must be admitted "that the condition of visceral ptosis favors their formation." However, there can be no doubt that the altered relation of the bile ducts and organs, especially the right kidney, the liver, and the duodenum, might in a variety of ways cause obstruction to the outflow of bile and thus induce jaundice.

PATHOLOGY.—It may be well before taking up the diagnosis of this condition to consider more particularly the pathology of enteroptosis. The symptoms of enteroptosis may be accounted for by various theories, which for convenience fall under three headings:

1. The mechanical theory of Glénard.
2. The neuro-mechanical theory of Meinert.
3. The neuro-intoxication theory of Schwerdt.

The first theory, though not a purely mechanical one, does not ask for any antecedent nervous cause, but implies a weakness of the suspensory ligaments of the transverse colon, especially the colo-hepatic ligament. The descent, Glénard claims, begins at the hepatic flexure and the other events incident to the disease follow—entero-stenosis, due to a kinking of the colon at the point of prolapse, the gastropotosis, the constipation, auto-intoxication, the neurotic manifestations, etc.

Under the second theory Meinert attributes the symptoms associated with dropping of the viscera to the constant stimulation and irritation of the sympathetic nerves, as a result of pulling and stretching of these nerve fibres. The blood-forming organs and the general nervous system participate in this abnormal irritation and stimulation, and chlorosis, neuroses, and a variety of vaso-motor disturbances are thus induced.

Schwerdt believes that the nervous system is primarily at fault; the fibre of the individual is toneless, the functions of the abdominal muscles, both parietal and visceral, are not normal; intra-abdominal pressure is lessened, ptosis follows. There is a stasis in the blood and lymph vessels, the bowel contents stagnate and decompose, excretions accumulate; absorption of poisonous products goes on, and intoxication is the result—dyspepsia, headache, anemia, palpitation, neurasthenia, etc.

DIAGNOSIS.—In the great majority of cases one may suspect the condition from the complaints made by the patient—digestive disturbances, distress, not necessarily pain, in the stomach on getting up in the morning, or after being in the recumbent posture for some time, dragging under the right costal margin, a feeling as if something falls over to the left side when the patient turns on that side, constipation, lack of energy, and other neurasthenic symptoms. The patient is generally slender and of lean habit.

An examination of the abdomen, however, is necessary to correct or justify the suspicion derived from the complaints. The contour of the abdomen may further suggest a condition of splanchnoptosis and inflation of the stomach by means of tartaric acid and bicarbonate of soda, or air cautiously pumped in, readily and accurately serves to locate that organ. The solid organs may be palpated, and it is recommended to examine the liver while the patient is in the upright position. Displacements of this organ are doubtless much more frequent

than might be supposed, judging from the results of examination in the dorsal position. The right lobe of the liver in some cases projects in a tongue-like process below the costal margin. It has been described as Riedel's lobe, and may occasionally be somewhat misleading. The test known as "l'épreuve de sangle," already described, should be applied in all suspected cases. It is scarcely possible, after a careful examination, to mistake enteroptosis for any other condition. Doubtless many

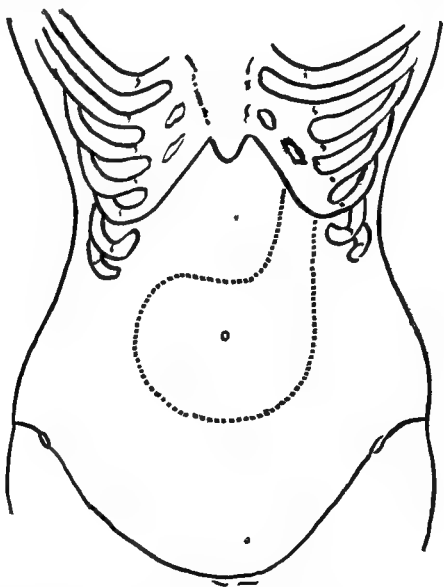


FIG. 5147.—From a Case of Pulmonary Tuberculosis. Gastropotosis with dilatation of the pyloric end, showing as a three-quarter circle; the umbilicus as centre.

cases of gastric neurasthenia and of nervous dyspepsia would be cleared up by a careful search for visceral ptosis.

Among others at least two instances of mistaken diagnosis coming under the writer's notice may be recorded. In one, a diagnosis of malignant disease of the stomach led to a laparotomy revealing the pancreas as the palpable misleading mass, while in the other, recurrent jaundice was thought to be due to gall stones or a "sluggish liver," and the horseback riding, rowing, walking, canoeing, recommended for its relief, aggravated all the symptoms. On the other hand, there is danger of attempting to explain too many symptoms by visceral ptosis.

PROGNOSIS.—Many patients recover entirely, losing all symptoms and signs of the disease. The majority may recover from the evil train of symptoms, the ptosis existing in part at least. It may be fatal as the result of the exhaustion and intoxication in extreme cases.

TREATMENT.—The indications for the treatment of enteroptosis as originally recommended by Glénard can scarcely be improved upon. They are as follows:

1. The intestines must be elevated and kept in their new position.
2. The abdominal pressure must be increased.
3. The bowels must be regulated.
4. The secretions of the intestinal glands must be increased.
5. The digestion and nutrition must be regulated and stimulated.
6. The whole organism must be strengthened.

If a cause can be fixed upon as inducing or aggravating the displacement, let it be removed. Those measures will best meet all these requirements which increase the strength and raise the tone of the whole musculature. It seems in most cases to be a question of nutrition, rest, good food, mild yet efficient purgatives, or better still enemata, occasionally gastric lavage, with drugs directed

against fermentative processes in the early stages of the treatment, as indicated. It is of the highest importance to increase the strength of the abdominal muscles by regulated exercise. Belts, or abdominal supporters, so highly recommended and in such variety, are of doubtful utility. Only those belts which increase the intra-abdominal pressure should be used. They encircle the abdomen and exercise the same degree of pressure over the whole abdominal surface. It is not only futile, but often harmful, to attempt to hold a kidney or a stomach in place by any special device externally applied.

With respect to surgical treatment of this condition, it must be said that it should be undertaken only after other methods have failed, and then only with the greatest care, especially in those cases in which the neurasthenic element is strongly manifest, for such patients are often worse rather than better after surgical interference. Duret first operated in 1894, lifting the stomach and fixing the serosa of the lesser curvature of the stomach to the parietal peritoneum and muscle of the anterior wall of the abdomen. Byron D. Davis (1897), Beyea (1898), Hartmann (1899), Treves, Bier, and Webster, have operated with varied success on similar cases. Beyea and Stengel shortened the gastric hepatic omentum and gastrophrenic ligament by plicating with multiple sutures, thus bringing the stomach up to its normal position. Webster, selecting those cases in which there was separation of the recti muscles, sought to increase intra-abdominal pressure by resecting the fascia of these muscles and then suturing the muscles together.

William Fawcett Hamilton.

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ERYTHROL TETRANITRATE, $C_4H_6(ONO_2)_4$, is obtained by the action of nitric acid on the tetramitic alcohol, erythrite, a substance found in several different lichens, especially *Rocella*. It occurs in colorless lamellæ, melts at $61^\circ C.$ ($142^\circ F.$), is insoluble in water, and dissolves readily in alcohol and ether. On percussion or when rapidly heated it explodes with great violence, and one fatality has occurred from its trituration with sugar of milk. In direct sunlight it turns yellow and gives off nitrous fumes.

The drug is a vaso-dilator, and its action differs from that of amyl nitrite and nitroglycerin in no essential except that it is slower in its onset and more lasting. It is said to take half an hour for the production of vaso-dila-

tation, and several hours for the effect to wear off. The dose is gr. $\frac{1}{4}$ -i. (0.015-0.06 gm.), most conveniently administered in tablet triturates. Bradbury recommends 3 i. (4 c.c.) of a 1 in 60 alcoholic solution repeated every four to six hours.

W. A. Bastedo.

ERYTHROMELALGIA.—This affection was originally described by Weir Mitchell in 1872 as follows: "A chronic disease, in which a part or parts—usually one or more extremities—suffer from pain, flushing, and local fever, made far worse if the part hangs down," and writers since then have not been able to agree upon a definition more satisfactory than this descriptive one. Up to the present time about one hundred cases have been reported and discussed by neurologists and pathologists, the questions of its pathogenesis, and of whether the affection is properly a distinct disease or entitled only to be called a group of symptoms, having excited much interest. To these topics we shall return in their proper place.

The subjects of erythromelalgia are usually middle-aged people, sometimes young adults, but seldom children. Many more males are attacked than females, and the predisposing causes are such as men are more liable to than women, viz.: occasionally traumatism, as from a stone falling upon the foot, exposure to wet and cold, especially when repeated, long standing at fatiguing work, sometimes exceptionally exposure to heat, as in working at a furnace. Also malaria, syphilis, anæmia, alcoholism, hysteria, and dyspeptic states are all believed to stand in a causative relation to it. It is also found associated with various other general diseases, and particularly those of the nervous system. Reynolds mentions one case as coming on suddenly soon after confinement.

SYMPTOMS.—The most distinctive and fundamental symptoms are those originally emphasized by Weir Mitchell. He also in his most recent paper on the subject reminds us that the pure type of symptoms should be looked for in the youngest class of patients, for in those who are more advanced in life diseased conditions of the arterial or nervous system may exist independently of erythromelalgia and lead to confusion. The local symptoms involve almost exclusively the peripheral parts of the extremities. The three characteristic symptoms are localized *pain*, *redness*, and *swelling*, suggestive of inflammation and yet to be carefully discriminated from it. The *pain* is apt to be the first abnormality to attract attention, involving most frequently the great toe, the heel, the ball of the foot on its inner or outer side, or the metacarpo-phalangeal articulation, less frequently the upper extremities, or exceptionally other parts. These pains are described as burning, irritating, piercing, and as sometimes of intolerable severity, "as if the part were being destroyed by fire" (Kahane). They are at first occasional, coming on at varying intervals or after special exciting causes; then they become intermittent and then constant, although there are reports of cases in which they finally ceased. The latter part of the day, especially after exhausting labor, hot weather, a hanging position, also motion, all intensify the suffering; while on the other hand cold, either of the weather or of applications, rest, and an elevated position of the affected part give relief. Thus it is quite characteristic for patients when the hands are the seat of the local trouble to carry them crossed upon the chest or raised above the head (Barlow).

The *redness*, which is the second prominent local manifestation, accompanies the pain, and its tint is variously described as fire-red, violet, livid, the latter verging sometimes into a cyanosis. Weir Mitchell calls it rosy red and congestive, and the disease itself has been called *red neuralgia*.

The *swelling* comes on gradually, is localized like the pain and redness, especially about the joints, but is not marked by pitting. It is increased by motion. Nor is it strange that this association of symptoms has in some cases led to a diagnosis of deep-seated inflammation, for

the relief of which incisions have been made, which, however, revealed nothing.

The seizures thus characterized were called by Mitchell "vascular storms." They may last for several hours or may extend to days or weeks, the local feature sometimes extending to parts not originally involved. The seats of attack are sometimes symmetrical, sometimes not. But in addition to the symptoms already mentioned others show themselves, which have been considered not characteristic of erythromelalgia, and which are not constant, but still may be of importance as bearing upon its pathogenesis. Thus Elsner and Barlow speak of hyperidrosis accompanying the paroxysm, of "innumerable droplets of perspiration standing upon the skin at the time of the most acute pain." There may be a condition described as local asphyxia, which may merge into cyanosis. The pulse is often quickened, which, taken in connection with the changes in the circulation, may be an index of more than local vaso-motor disturbances. Lesions of sensibility are frequently present, hyperæsthesia and paræsthesia most commonly, but are by no means constant enough to be regarded as characteristic of the disease; nor is the motor function often interfered with, the lesions when occasionally encountered in the more advanced cases being present as weakness and paresis. There is sometimes muscular atrophy. Reflex irritability is infrequent. The *trophic* lesions associated with the local manifestations are frequent and multiform. The skin may be either thickened or show changes analogous to the "diffuse idiopathic atrophy of the skin," of dermatologists, as in a case reported by Schütz. There are sometimes pigmentation and œdema, and lumpy alterations of the joints and nails; also rhagades and ulcers may develop. It is also quite common to find nodules or papules on the reddened and painful areas (Kahane). One other symptom which sometimes presents itself is gangrene, considered by some to be a feature of indubitable cases of erythromelalgia, its occurrence depending upon the greater or less severity of the disease (Sachs), and by others as indicating its alliance with Raynaud's disease.

Such, then, are the local changes, which, says Reynolds, are the only symptoms in twenty per cent. of the cases. The disease is essentially chronic and of very gradual development. Barlow refers to one case which lasted for twenty-seven years, the affection limited to the sole of one foot; Elsner to one involving the left index finger only, for sixteen years, amputation of the finger finally relieving all the symptoms.

Interesting as erythromelalgia has proved to neurologists, it is its pathological position which has given rise to the most discussion, for its symptomatology is well recognized and its diagnosis not ordinarily attended with difficulty. Still there have been but few autopsies reported. The opportunity of examining amputated parts has indeed been availed of, but the findings have not led to general agreement as to its pathological anatomy, and Cassirer, writing in 1901, says: "We are still to-day far removed from any certain knowledge of the pathological anatomy of erythromelalgia." Consequently its pathogenesis has not been satisfactorily determined. Nor have the questions whether it is ever an idiopathic disease, or whether it is merely a "symptom complex," associated with various other diseases, been answered conclusively. It would be impossible here to go into the details of this inquiry, and it has seemed best to give as nearly as possible in chronological order the views of the principal authorities, which will at all events show the trend of professional opinion and develop the mooted points.

Weir Mitchell in his earlier publications refrained from any positive expression of opinion as to the origin of the malady, but later (1878) regarded it as "a *vaso-motor neurosis*, which might occur either independently or in association with spinal or cerebral disease, where some distinct lesions of definite regions might ultimately be discovered." Subsequently he expressed the view that in erythromelalgia a neuritis of the finest nerve twigs may be present. Lewin and Benda, writing in 1894,

most thoroughly discussed all the cases that had been reported up to that time. They classify these cases under three headings: 1st. Erythromelalgia in organic diseases of the central nervous system. 2d. In functional diseases of the central nervous system (neuroses). 3d. As a peripheral affection (neuritis and neuralgia), the latter group embracing half of all the cases. The vaso-motor symptoms are always secondary to the neuralgic pains. In answer to the question whether it is an independent disease, their conclusion is that it is not a disease *sui generis*, but may be associated with various peripheral and central diseases of the nervous system.

In 1895 Eulenburg wrote that he had reasons for "thinking that the starting point of the disease may be found in certain sections of the gray axis of the cord, especially in the posterior and lateral gray substance, and the associated fasciculi," an opinion which has had great weight.

Auerbach in 1897 published a report of the first complete autopsy made on a case of this disease. There was a normal condition of the peripheral nerves and spinal ganglion cells, marked degeneration of numerous radical fasciculi (Wurzelbündel) in the cauda equina, on one side more than the other, belonging to the first or second sacral nerve and the last lumbar nerve. Pronounced ascending degeneration in the cord."

In 1899 Weir Mitchell and Spiller report that in examining an amputated toe from a patient with erythromelalgia there were found a high degree of degeneration of the nerves, which were almost completely converted into connective tissue, also extreme changes in the vessels, thickening of the media, hypertrophy of the intima, and in places complete closure of the lumen of the artery; and on this finding peripheral neuritis was assumed as the basis of the disease. In this article the opinion is still held that certain cases may be due to some form of spinal disease, but the idea of a nerve-end neuritis is urged. These examinations and others give greater definiteness to the discussion of the pathological relations of the central and peripheral organs in the development of the disease. In Dehio's case 4 cm. of the ulnar nerve and an equal length of the ulnar artery were removed just above the wrist for erythromelalgia involving the hand. The little finger improved, but the rest of the hand remained unchanged. Examined under the microscope the piece of the nerve was found normal, but the artery showed marked arteritis of the middle and inner coats and some diminution of the lumen. Barlow indicates three directions in which inquiry as to the pathology should extend: 1st, to the peripheral nerves; 2d, to the brain and cord, especially in regard to the vaso-motor centres; and 3d, to the blood-vessels. He declares that the disease has been generally regarded as a vaso-motor neurosis or paralysis, and concludes that "in the absence of obvious nerve disease to explain the arterio-sclerosis we are led back to the hypothesis that the chief fault lies with the vaso-motor centres and their abnormal efferent vaso-motor impulses leading to dilatation of the vessels and consecutive disease induced thereby. Some peripheral strain or irritation may have been transmitted to the vaso-motor centre as the original cause of the disturbance." He further expresses the belief that probably the change in the vaso-motors starts centrally, especially in the generalized cases of the disease, although it is more reasonable to suppose that in uncomplicated cases the primary change starts at the periphery. The question whether erythromelalgia is an idiopathic affection or should be considered merely a group of symptoms appearing in association with various primary diseases has brought out a diversity of opinion. Collier in 1898 says it is not now regarded so much as an idiopathic disease as a group of symptoms occurring in other affections, and Kahane, writing in 1900, quotes Lewin and Benda, Eulenburg and Levi as holding the same view, and says the conclusion reached in all the larger comprehensive statements about erythromelalgia is that it is no individual disease, but a symptom-complex accompanying various other diseases of the nervous system.

Kahane himself, however, finally gives as his own opinion that it should be ranked among the acropathies, which he defines as those affections which are localized in the peripheral parts of the limbs and as the ultimate basis of which are assumed lesions of a vaso-motor nature. There is great difficulty in determining whether the nerves or the vessels form the starting point, whether we have to do with an irritation of the vaso-dilators or a paralysis of the vaso-constrictors. He says, in conclusion of a long and careful consideration of the question, that there are two points that one can be sure of: 1st, that erythromelalgia belongs clinically to the group of acropathies; 2d, that it is to be referred to a disturbance in the relation between the systems of the nerves and blood-vessels quite without regard to the question whether it is of functional or anatomical, central or peripheral nature. In his conception it is a phase of disease that occurs in one series of cases independently and in another as an attendant phenomenon of other diseases.

Sachs had found the blood-vessels diseased in most cases, but the nerves not in many; the changes in the latter he believed to be secondary. He says erythromelalgia occurs as an independent group of symptoms, even if not an individual disease. In uncomplicated cases it is probably to be referred to disease of the peripheral arteries. The obliterating arteritis may be indirectly connected with central disease, but may be wholly independent of such influences. In 1901, Elsner, on examination of the arteries in cases that he saw, found them the seat of occasional slight thickening of the intima, but the nerves normal. He calls attention to several cases in which gangrene of the extremities occurred. He believes that erythromelalgia cannot at present be defined as a disease *per se*. Cassirer, on the contrary, is constrained to place himself among those who believe the disease to have a certain idiopathic character, while recognizing like others one class of cases of a peripheral and a second of a central origin. Allchin and Saville regard the disease as of vaso-motor origin, probably allied to Raynaud's disease, the former speaking of it as an expression of vaso-motor ataxia. Shaw in 1903 analyzes nine cases and reports the results of the examination of amputated toes in three cases, stating that "vascular change was present in all, mostly an increase in the intima of the arteries and occasionally thrombosis and changes in the inner coat of the veins. The nerves were investigated even to their terminations, and no degeneration was found, nor was there any suggestion of increase of fibrous tissue in the trunk of the nerves." (Compare Mitchell.) He says: "In no case has recent degeneration of nerve fibres been demonstrated, and in not one of the nine cases analyzed was anæsthesia ever present." He concludes that erythromelalgia when occurring independently of central nervous change is associated with but one morbid picture, that of local vascular change. Taubert finds erythromelalgia traceable to disease in the lateral and posterior columns of the cervical cord (see Eulenburg and others). Reynolds calls the disease a vaso-motor neurosis, and argues in favor of the theory of primary vaso-motor dilatation of the arteries followed in the way of compensation for this vaso-motor paralysis by thickening of the coats of the arteries so as to narrow the lumen and stream of blood (quoting Delafield, Thoma, and Barlow in support of his views). Starr, sketching the phenomena of the "vascular storm," says: "The dilatation of the arteries in the extremities results in an extreme condition of redness and sensation of heat and pain. After hours of this the extremities may suddenly become cold, pale, or blue and shrivelled up, presenting the appearance of the hands after long soaking in hot water; and this alternation of distention and contraction of the blood-vessels constitutes the symptomatology of the disease. It appears to be a pure vaso-motor neurosis, but it is rarely if ever attended by any trophic disturbances of the skin or nails, such as occur in neuritis, and no pathological observations are at hand to establish the hypothesis that there is a true neuritis of the vaso-motor nerves."

If, therefore, we should venture upon a rough summing

up of the principal pathological features of erythromelalgia as indicated in the preceding brief synopsis of recent authorities we should say that opinion was settling upon the following beliefs: (1) The disease is considered a vaso-motor neurosis (angioneurosis, Oppenheim); (2) the attribution of the group of symptoms to disease of the posterior and lateral spinal gray matter, when it would be called secondary, and to as yet undetermined causes of peripheral origin, where some would call it clinically idiopathic or *sui generis*; (3) its association with the acropathies and sometimes with Raynaud's disease; (4) there is much more evidence connecting the disease locally with alterations of the blood-vessels than of the nerves, but good authorities deny that we are yet in position to pass finally upon its pathology.

The TREATMENT of erythromelalgia can hardly be said to aim with hopefulness at more than the alleviation of some of its most distressing symptoms, proof of which is found in the long list of the various means employed. Weir Mitchell's recommendation of rest, cold, and elevation of the limb affected has been found of value, based as it is upon well-known observations of patients that the opposites of these increase their sufferings. Other measures to be noted are hydrotherapy, electricity (Eulenburg and Schütz found benefit from the use of the constant current), massage (although Barlow says it is of doubtful value and unbearable during the paroxysms). Of course antisyphilitic remedies are indicated in cases in which that disease is believed to underlie or complicate erythromelalgia, and among drugs which are more or less approved are arsenic, antipyrin, the bromide of potassium, morphine (Morgan reporting a case of recovery after hypodermic injections of morphine and atropine twice a day for three weeks), the salicylates, atropine, and ergot internally as well as ichthyol externally. It should also be remembered that spontaneous recovery has taken place in some cases. Further than this, the several cases referred to above are evidence that surgical measures, such as the stretching of nerves, their resection, and the amputation of toes and fingers, have brought relief in certain instances. It should be noted, however, that gangrene followed operative procedures upon nerve and vein in one case of Weir Mitchell's and upon amputation of a toe in another.

The references given below are mainly to the chief articles of the last three years, the reader being referred to the essays of Lewin and Benda and of Kahane for full bibliographies.

J. Haven Emerson.

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EUCAINE is a name applied to two different but closely allied local anæsthetics distinguished as *Alpha-eucaine* or *Eucaine "A"* and *Beta-eucaine* or *Eucaine "B"*.

The anæsthetic effect of cocaine, which is methyl-benzoyl-ecgonine, $C_{17}H_{21}NO_4$, was found to depend on the presence of both the methyl and the benzoyl groups and not on the ecgonine radical. So with the desire of obtaining the anæsthetic effect of cocaine without its toxicity, other methyl-benzoyl compounds were designed. Of these Eucaine "A" was submitted to the profession, and was for a time extensively employed; but its very irritating effects have so militated against its desirability that it has been largely replaced by its congener, Eucaine "B," a compound of less toxicity and less irritating properties.

Alpha-eucaine, $CH_3.N.C_2.(CH_3)_2.(CH_2)_2.(CH_2)_2.CC_6H_5.CO.O.COCH_3$, is methyl-benzoyl-tetra-methyl-hydroxy-piperidine-carbonic-acid-methyl-ester, a derivative of tri-acetone-amine. Its hydrochloride occurs as a bitter white crystalline powder soluble in 10 parts of cold water, 7 of boiling water, less than 2 of alcohol, and 13 of glycerin, and is very slightly soluble in ether and the fixed oils.

Beta-eucaine, $H.N.C_2.HCH_3.(CH_3)_2.(CH_2)_2.C.C_6H_5.CO.O.H$, benzoyl-vinyl-diacetone-alkamine, is also a bitter white crystalline powder, and its hydrochloride dissolves in 23 parts of water, 12 of boiling water, 30 of alcohol, and 35 of glycerin. It is insoluble in ether and almost insoluble in the fixed oils.

Both eucaines have the nature of alkaloids, and their hydrochlorides have been the salts in common use; but the acetate of beta-eucaine is now recommended as it is readily soluble in water. The solutions of eucaine salts are not decomposed by boiling, so may be sterilized.

The pharmacological action of the eucaines has been studied by Cushny, Vinci, Ver Eecke, and others. The salts are not absorbed by the unbroken skin, but, applied to mucous membranes or injected into the tissues, they paralyze the sensory nerves and their terminal endings at the site of application and are powerful local anæsthetics. They are said to produce local congestion in mucous membranes.

In large dose they weaken the heart by direct depression of the cardiac muscle and its contained ganglia, and in addition lower blood pressure by dilatation of the arterioles. The respiratory centre is at first stimulated, later paralyzed, so that death takes place from asphyxia (paralysis of respiration). The cerebral centres are stimulated with the production of tonic and clonic convulsions; later they are paralyzed. There is no dilatation of the pupil or disturbance of the accommodation of the eye, but the conjunctiva is congested. The superficial epithelium of the cornea is not affected. The kidney cells are stimulated and the quantity of urine is increased, with increased elimination of nitrogen, phosphorus, and chlorides. The drug is not found in the urine, and apparently undergoes decomposition in the body.

To produce general poisoning in rabbits and guinea-pigs it requires 0.15–0.2 gm. of eucaine "A" per kilo, and 0.4–0.5 gm. of eucaine "B." Cocaine is four times as poisonous as eucaine "B," and only slightly more toxic than eucaine "A."

The uses of beta-eucaine as a local anæsthetic are practically those of cocaine, so we need not here enumerate its therapeutic applications. The consensus of opinion among surgeons (Bier, Bainbridge, Moyer) would seem to indicate that it is weaker as an anæsthetic than cocaine, whether employed subcutaneously or in spinal analgesia. Wallis found that the amount required for a small operation averaged 3 i.-ss. (4–6 c.c.) of a four-per-cent. solution, but G. W. Crile performed a painless duodenostomy with 8 c. (3 ij.) of a two-per-cent. solution.

Nearly all writers agree that eucaine tends to increase a hyperæmia of the conjunctiva or nasal mucous mem-

brane, and Dawbarn and others prefer it for the removal of tonsils, adenoids, and other hypertrophied tissues, as it does not cause a shrinkage like cocaine. Poole prefers cocaine in iritis, as eucaine increases, or at least does not decrease, the anterior congestion.

In our experience eucaine applied to mucous membranes is slower in its action and much weaker than cocaine; used subcutaneously it is somewhat weaker. We had several cases of local gangrene following its hypodermic use in abdominal and pleural tapping, though in each of these instances the injection had been preceded by the ethyl-chloride spray. Cocaine under similar conditions never produced a slough. Da Costa noted a slow, persistent sloughing, especially in fatty tissue, bursæ, or tendon sheaths. He also noticed inflammation following its use in the bladder. Shastid reports the occurrence of amblyopia, rapid pulse, and delirium following the application of a five-per-cent. solution to the inferior turbinate.

Beta-eucaine is, then, a drug of anæsthetic action resembling that of cocaine, but somewhat weaker. It produces hyperæmia rather than the ischæmia of cocaine, and has no effect on the pupil, accommodation, or the corneal epithelium. In the ordinary dosage it is non-toxic, and is reported to be well borne where there is an idiosyncrasy against cocaine. Lilienthal has frequently used four to ten grains without unpleasant consequences. No eucaine habit is known. The drug keeps indefinitely and can be sterilized by boiling.

Solutions of one- to four-per-cent. strength in normal salt are commonly employed, but stronger solutions, obtained by heating the liquid and using warm, are sometimes preferred. Von Mikulicz uses the following: \mathcal{R} Cocainæ hydrochloridi, 0.5 gm. (gr. viiss.); beta-eucainæ hydrochloridi, 0.5 gm. (gr. viiss.); sodii chloridi, 2 gm. (gr. xxx.); aquæ, q.s. ad 1,000 c.c. (\mathcal{Z} xxxii.).

W. A. Bastedo.

EXOPHTHALMIC GOITRE.—(Synonyms: Graves' disease; Basedow's disease.) These names have been indifferently used during the last sixty or more years to express a fairly well-defined disease in which more or less enlargement of the thyroid, protrusion of the eyes, and certain nervous disturbances (including tachycardia) form the prominent symptoms. The Irish physician, Graves, who described the coexistence of palpitation of the heart with enlargement of the thyroid as an affection more or less related to hysteria, was antedated in his observations by Parry, who mentioned the same combination together with exophthalmos in 1825. Some years later Basedow also observed the existence of exophthalmos in similar cases, and gave the description which has connected his name with the disease. Charcot, too, in 1844 and 1845 described such cases at the Salpêtrière. Since their time an enormous literature has appeared in which, while the objective descriptions remain very constant, the most divergent theories have been advanced to account for the symptoms. These we may detail in discussing the etiology of the disease.

Exophthalmic goitre is an affection which occurs most frequently in women, although cases are by no means rare in which the same phenomena are seen in men. No very precise age limits can be set, but the majority of the cases appear to begin after the age of puberty, and to increase in number as the climacterium is approached, the onset being most frequent, according to Osler, between the ages of twenty and thirty. No particular station in life seems to predispose to the disease, but it is usually observed that the individuals belong to neuropathic families in which cases of epilepsy, hysteria, chorea, or even some form of insanity have occurred. Combinations of epilepsy and exophthalmic goitre in the same person have been described,¹ in which cases the epileptic seizures usually give place to the symptoms of the other disease. Exophthalmic goitre is a very widespread disease, not at all localized in certain areas, as is the case with other forms of goitre and with endemic myxœdema or cretinism. Indeed, although cases in which exophthalmic

symptoms supervene after the long existence of the ordinary type of goitre are not unknown, the disease seems to be no more frequent in those regions where goitre is endemic than elsewhere, and the coincidence of the two conditions must be considered accidental. Instances of the coexistence of exophthalmic goitre with myxoedema have also been observed,² which, although probably accidental and not indicating any close relationship between the two conditions, have a significance which will appear later.

SYMPTOMS.—The onset is sometimes very slow and gradual, in other cases it is extremely sudden, and the symptoms reach their maximum of intensity in a very short time. Usually, but not always, such an onset is ascribed to sudden violent emotional disturbances, such as a fright or great mental strain, etc., after which the patient feels demoralized and incapable of effort, and the palpitation of the heart and tremors begin. Prominence of the eyeballs may be the first thing observed, and is noticed by the friends before the patient herself appreciates it.

Of all the symptoms perhaps the most constant are those referable to the heart and circulatory system in general, and these may be considered under several heads. First of all and most noticeable is the violence of the heart's action—a pounding heart beat, that may sometimes be violent enough to keep the patient awake, can be felt over a wide area. Loud systolic bruits can often be heard over the apex and base of the heart and along the vessels. The pulsation of the arteries is extraordinarily violent in many cases and is readily visible in the extremities. There is usually a widespread dilatation of the capillaries also, and sometimes a venous pulsation can be made out. The dilatation and violent pulsation of the vessels are especially noticeable over the enlarged thyroid and in the eye grounds.

Then next in prominence is the tachycardia, which may reach the highest degree. Usually this develops gradually and the pulse rate increases from normal up to 130 to 150 or more in the minute. In a case recently observed in the Johns Hopkins Hospital, a rate of 200 per minute was maintained for days. The tension in such cases usually remains high, and the volume full. F. Müller³ gives a sphygmographic tracing in a case whose pulse rate at the time was 176, in which this is illustrated, there being a sharp initial elevation with frequent bigeminal pulsation. Recent researches seem to show (Donath,⁴ Spiethoff⁵) that the blood pressure is in some cases increased, in some diminished, but by no means always increased.

Variations in the pulse rate are very marked, and excitement or exertion has a much greater influence than in a normal individual. In some instances it is impossible to escape from the idea that exhaustion of the heart muscle must play a part in the final dissolution of the patient.

Referable to the central nervous system more directly we find a variety of symptoms, of which perhaps the most prominent is the tremor. This is involuntary and fine for the most part, leading to a rapid trembling of the hands, muscles of the face, and indeed of any and all of the muscles indifferently. It is most noticeable to the patient in the attempt to perform delicate co-ordinated movements. Writing becomes difficult or impossible, and the characters show a tremulous irregularity. Fibrillary twitchings of the tongue are usually present, and may be so extensive as to produce a wave-like undulation over the surface of that organ.

The other symptoms referable to the nervous system are chiefly psychical. Early in the disease the patients feel themselves to be irritable and excitable. The friends observe a change of disposition, very different from that observed in the development of myxoedema. Instead of becoming sluggish and apathetic, with all the mental faculties dulled, these patients are keenly susceptible to every outward stimulus, and the mental reaction is a relatively intense one. In some respects this receptive and reactive state may resemble in a mild way

that seen in the maniacal stage of the maniacal-depressive insanity. A feeling of anxiety often dominates the mental state, and the excited patient becomes a prey to groundless fears. Insomnia may be persistent, leading to great exhaustion. In other cases fantastic dreams occur with great frequency, and may pass over into the waking state, so that the patient has but to shut her eyes to see all sorts of forms move about her, or even in broad daylight the hallucinations may occur. Delirium and the wildest maniacal excitement, or stupor and even unconsciousness, may come on late in the disease.

The exophthalmos is not an invariable feature, although it is very frequently present (Fig. 5148, A and B); it may be unilateral, but is usually bilateral. In its onset it becomes, as a rule, gradually more and more noticeable, but sometimes, as it is alleged, after a sudden emotional shock it may appear and reach a high grade within a very short time. The actual extent of the protrusion of the eyeball it is difficult to measure, although methods have recently been devised which will render such measurements more exact. It is most noticeable in the widening of the aperture of the lids which it produces, and by the staring expression which it gives to the face; but it must not be forgotten that the individual variations in normal people in this respect are very great. In extreme cases, however, such as one of Basedow's, the eye may be actually dislocated from the orbit. In most cases it is possible to press the eye back into its original position during the earlier stages of the disease, but this may become impossible later. Many consequences of this protrusion have been noted in the literature, and as signs of the exophthalmos they bear the name of their observers. Von Graefe, for example, noticed that in lowering the eyes the upper lid did not follow and keep the sclera covered as in the normal eye—the so-called von Graefe's sign. Stelwag's sign consists in the widening of the palpebral aperture; Möbius' sign, in the lack of normal convergence of the eyes. Other phenomena, such as the absence of wrinkling of the forehead on raising the eyes, and the change in the ease with which the upper lid may be everted, may be mentioned.

Pupillary changes are rarely if ever seen, and no definite retinal alterations have been found, nor is there any disturbance of sight from the exophthalmos proper. Winking is much less frequently carried out, however, than in the normal eye, and in cases in which the eye projects far from its socket the eyelids never quite cover the eyeball. The consequence may be that the proper moistening of the surface is interfered with, and a band-like area across each eye, passing over the cornea, becomes dried and opaque. Ulceration and infection of this dried area, which becomes wider with the increased protrusion, leads to complete opacity of the cornea and loss of vision in that eye. The infection may even go on to involve the whole eye and result in its entire destruction.

The absence of pupillary disturbances is particularly significant in connection with one of the theories as to the etiology of the disease, as will appear later.

No special disturbance of the urinary secretion seems to occur with this disease, although glycosuria has been observed in some cases and polyuria in others.

Digestive disorder and disturbances of the general metabolism, however, are almost constant, and have an extremely important bearing upon the prognosis.

Loss of appetite is very common, and the patients waste away perhaps as a result of this. On the other hand, a ravenous, insatiable appetite is sometimes observed, but strangely enough with the same progressive emaciation. F. Müller⁶ describes most graphically this curious phenomenon: "The food prepared for this patient, quite enough for the nourishment of a robust person, was not enough for her, and she gathered up every scrap of food that was left by the other patients in the ward. One found her almost always eating, and it was curious to see her, as with wide-open, eager eyes she

stared into her plate and ceaselessly chewed and swallowed."

There are, however, variations in this emaciation, such that, while at times the patient loses rapidly in weight, there come periods during which she recovers almost all that was lost, and Huchard speaks accordingly of "*crises d'amaigrissement*." The loss of weight may be enormous and astoundingly rapid. One of Müller's patients lost fifty pounds in nine months, reaching then a weight of fifty-four pounds. Curiously enough the emaciation may not be general but limited to one portion of the body, either to one side or to the upper part, while the lower extremities remain unaltered. Von Schrotter⁷ describes such a case in which the very fat legs contrasted sharply with the wasted chest and shoulders.

Diarrhœa, of a most persistent character, is often observed, and may aid greatly in producing the emaciation. It seems possible that it may be due to an increased activity of peristalsis dependent upon some such nervous influence as produces the general tremor. Studies of the metabolism in exophthalmic goitre by Müller and others tend to show that while the assimilation of food proceeds normally there is an extraordinary increase in the excretion of nitrogen and other substances, notably phosphates, while the absorption of oxygen in greatly increased quantity indicates the augmentation of oxidation processes.

Symptoms from the genital apparatus are very inconstant and difficult to explain. There is sometimes a cessation of the menses, and there have been instances in which pregnancy has had a favorable influence upon the course of the disease.

Changes in the skin are frequent and of many sorts.

sensations of heat, accompanied by flushing of the skin, frequently occur, while the general temperature is normal. Other changes, difficult to explain, also appear, such for example as the extensive pigmentation of the skin, which may be almost like that observed in Addison's disease. An instance of this is the above-mentioned case of von Schrotter. So, too, urticaria, erythema, localized œdema, scleroderma, loss of hair, swelling of joints, atrophy and hypertrophy of breasts, etc., occur, and are usually explained as dependent upon disturbances of the trophic nerves.

Dyspnœa and labored breathing may come on, especially after exertion, and occasionally there is a dry cough which is very wearing, but which seems not to depend upon any actual pulmonary lesion.

Finally the thyroid shows fairly constant changes, which are recognizable clinically (Fig. 5148, A and B). The enlargement is usually diffuse and bilateral, but may not be extreme. Frequently it is so slight as to be hardly noticeable.

In all cases, however, the thyroid is somewhat increased in consistence and may sometimes become very hard. The vessels which course over it are generally widely dilated and pulsate violently, and to this great vascularity and hyperæmia is due in large part the enlargement of the gland.

PATHOLOGY.—Numerous autopsies have been performed on these cases, and the most painstaking examination of the viscera made, but as yet the constant lesions are very few. Especial attention has been directed to the nervous system and to the thyroid, and the description of the changes in these can therefore be made more minute.



A.



B.

FIG. 5148.—Case of Exophthalmic Goitre showing Exophthalmos and Goitre. A, Front view; B, side view.

Very characteristic is the profuse and continued sweating, which is no doubt due to the central irritation of the secretory nerves. It is frequently such as to bathe the patient constantly and to keep the skin in a sodden condition, from which results the increased electrical conductivity noted by Charcot and others. Annoying

In the central nervous system no definite constant changes have been discerned in the cerebral cortex nor in the lower portion of the brain or cord. Only Mendel⁸ and his students have found atrophy of the corpus restiforme on one side with a similar atrophy of the solitary bundle on the other side, and this he brings into causal

connection with the disease. It is, however, far from constant, and it is hard to explain a general condition by a one-sided lesion.

The sympathetic ganglia in the neck have also been examined with great care, but Ehrich,⁹ who from his



FIG. 5149.—Exophthalmic Goitre. Thyroid lobe in section from case illustrated in Fig. 5148.

cases was able to find degenerative changes, thinks them entirely secondary. Others find no alterations whatever in these ganglia and nerves, and in several cases which we have examined these structures have been quite normal anatomically.

Müller found degenerative changes in the trunk of the vagus nerve, but decided that these were secondary.

The alterations in the heart are by no means constant nor characteristic. Dilatation is sometimes found at autopsy, hypertrophy occasionally, while degenerative changes are frequent.

It is in the thyroid that the most characteristic and constant changes are met with. The gland is usually but not always enlarged, and its consistence much increased. No adequate idea of the vascularity is gained from the inspection of the specimen after death, but at operation it is found to be extraordinarily rich in widely distended vessels, which pulsate violently, and which from the friability of their walls (Kocher,¹⁰ Ehrich¹¹) render the operation for the extirpation of the gland a difficult one. The surface is often somewhat nodular and the capsule thickened. Section of the gland shows that it has not the translucency and brownish-red color of the normal gland, nor its gelatinous elastic consistence. Instead it is hard and resistant, and of an opaque pinkish-gray color, the cut surface having a rather lobular, roughened appearance. (Figs. 5149 and 5150.)

Usually the change is diffuse throughout the whole gland, but sometimes one lobe may be much larger than the other, and in some cases the alterations described are present only in small patches here and there throughout a gland which otherwise seems nearly normal. These foci are easily distinguished by their fine grain and by their opacity from the adjacent colloid-holding tissue.

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Apparently this represents a stage in the development of the lesion, and in most of the cases which show it the symptoms had existed only a short time before the operation. Microscopically the altered areas are quite sharply demarcated from the rest and may involve a great number of alveoli or be limited to very small foci, including only a few alveoli here and there. It is difficult to understand why the lesion should appear thus in certain areas only.

Microscopically there is usually made out a great increase in the connective tissue throughout the gland. Strands of fibrous tissue run through it from the capsule and produce a sort of indefinite lobulation. The alveoli are no longer rounded, full of colloid, and lined with low cubical epithelium, but are extremely irregular in size and in form. As a rule most of them are smaller than normal, while in the central part of each small lobule there are larger alveoli of very irregular outline, sending out diverticuli in every direction and encroached on by epithelial projections which extend into their lumen. With some special method of staining the connective tissue it may often be made clear that such a small lobule is probably a sort of colony in which the smaller peripheral alveoli are derived from the more centrally placed or are actually merely sections of the diverticula of the central ramifying alveolus. This alternation of large irregular alveoli with small ones ranged round them is very characteristic and evidently results, in part at least, from the separation of portions of the central cavity in the form of new alveoli. By many authors papillary outgrowths from the walls have been described, but Ehrich claims that these appearances are merely due to the irregular line of section of folds in the wall.

There is much variation in the size of the alveoli, the distended irregular ones being frequently long drawn out and sometimes even communicating with one another, while others are small and so packed with cells that there is no real lumen.

The epithelium becomes columnar not only in the

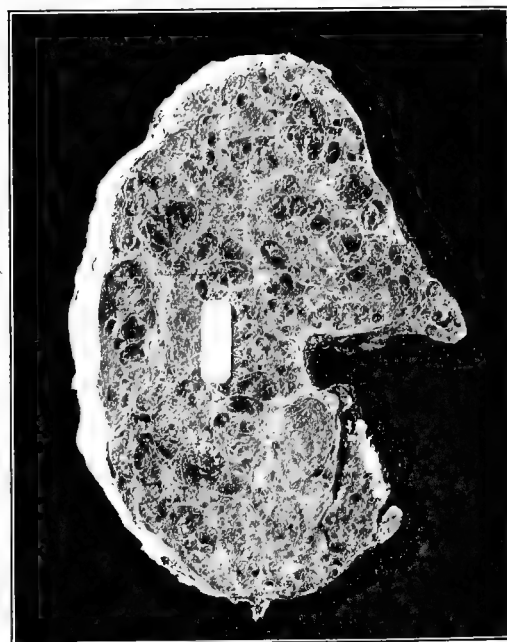


FIG. 5150.—Adenoma of Thyroid, or Colloid Goitre.

large alveoli, but in the small ones as well, and thus occupies so much space that there is but little lumen left. Indeed, the areas occupied by the small alveoli may appear almost solid, so small are their cavities and so scant

the colloid. In most instances the epithelium is very regular in its form throughout and the details of its structure can be made out very clearly. The cells are plump, with a finely granular protoplasm and a sharp outline. The free surface is sharply marked and is sometimes slightly dome-shaped. The nucleus may lie near the base or near the free end of the cell. Mitotic figures are frequently to be found. Occasionally some of the cells appear narrow and shrunken and biconcave in form, with very deeply stained nucleus and dark-red protoplasm. These are the so-called colloid cells of Langendorff, thought by him to be especially concerned in the secretion of colloid, but which seem to us rather more like the result of some degenerative process. Similarly the extensive desquamation of the epithelial cells which one so often sees in specimens removed at operation seems to be due to the considerable pinching and handling through which the specimen unavoidably passes during the operation. In many cases there occur in the midst of the altered thyroid circumscribed nodules which have the character of adenomata such as are seen in ordinary goitres—they are by no means peculiar to nor characteristic of exophthalmic goitre.

In nearly all the typical cases there are scattered about, usually in connection with the fibrous strands, masses of lymphoid tissue which are sometimes large enough to be conspicuous, opaque white dots visible in the fresh specimen. In one instance in which there was a cyst the numerous lymphoid nodules shone through the wall of the cyst very distinctly. In some cases they are small and indefinite in outline and are composed of an irregular accumulation of lymphoid cells. Generally, however, they are well-formed lymphoid nodules with very distinct germinal centres, composed of concentrically-arranged cells with abundant protoplasm. It seems probable that this increase in the bulk of the lymphoid tissue, which is practically invisible in the normal gland, is part of the general increase in size of the lymphoid structures which occurs so often, especially in the neck, but also in the thorax, abdomen, and retroperitoneal region. The superficial glands are usually not so much enlarged, but the lymphoid tissue in the pharynx, the tonsils, and the nodules in the tongue become very conspicuous. Microscopically it is found in all these places, as in the lymphoid nodules of the thyroid itself, that there is a great increase in the lymphoid cells, but also that the germinal centres become very large and sharply outlined and contain many actively phagocytic cells. The sinuses are usually filled with wandering cells. This change in the lymphoid tissue has the appearance of being a reaction to the absorption of some poisonous or injurious material.

We may pass over the histological details of the process of secretion as observed in these cases by Farner, Ehrich, Haemig, and others. Suffice it to say that while in some cases the process of secretion seems active enough, and the alveoli are filled with a stainable colloid material, in the majority the secretion of this stainable colloid is not evident, the cells have become high and vacuolated, and whatever secretion there is, is of the non-staining or chromophobe type of Andersson. The alveoli in these cases are empty of colloid, and contain only the debris of cells and fine ragged strands of granular material.

As to the removal of the colloid material from the gland there is still some doubt. Many authors have described the presence of a material staining like colloid in the lymphatics and interstitial spaces, while others have even declared its presence in the veins and arteries. Thus Farner¹² explains the lack of colloid in the follicles by the rapidity of its export. Ehrich, however, with right, suspects that the colloid-like substance in arteries and veins is merely the coagulated serum. Indeed he denies that any secretion escapes from the gland, and thinks the whole process a retrogressive one. Support is lent to Ehrich's views by the work of Oswald (*Virchow's Archiv*, 1902, 169), who finds a decreased percentage of iodine in the thyroid in exophthalmic goitre,

and considers the change a decrease in functional activity.

The thymus, too, has been found by nearly all investigators to be enlarged. There are not only the usual scanty remains, but the mass of tissue is frequently seen to be as large as or larger than that seen in a child before retrogression has taken place. Histologically it has the same appearance as in those earlier years, and the same processes of phagocytosis are seen to be going on. The recent statements as to its epithelial nature make this change in the thymus especially interesting and deserving of more attention than has been accorded it, particularly since there have been some favorable results from the administration of thymus extract in this disease.

The parathyroid glands are sometimes to be found attached to the portion of the thyroid extirpated at operation, even when the greatest care is exercised to preserve them. In other instances they were found at autopsy, and altogether we have had the opportunity of studying them in sixteen cases. They were practically normal in all the cases. The cells of all varieties found in the normal gland were seen in these, too, in the usual proportions. In six of the cases the notes state that there was an increase in the fibrous stroma, and renewed examination of these glands shows that there is in some cases a network of scar tissue running through the tissue, just as has been seen in the thyroid in so many of these cases. Otherwise, however, the tissue in these glands seems abundant and normal. On the whole it seems improbable that the parathyroids have anything to do with the production of the symptom-complex of exophthalmic goitre when we compare these very slight anatomical lesions with the advanced changes in the thyroid.

As to the hypophysis cerebri, there seem to be few recorded observations. Haemig studied it in nine cases and found it quite normal, although in several of the cases the number of chromophile cells was striking. In the one case in which we secured the hypophysis its tissue was normal.

The other organs show, as far as is known, no constant lesions. Askanazy has described certain degenerative changes in the voluntary muscle, but investigations confirmatory of his results seem not to have appeared.

ETIOLOGY.—Several distinct theories as to the etiology of the disease have been proposed, but they all fail to account satisfactorily for all the symptoms.

According to one, which has been defended by Buschan, exophthalmic goitre is a general neurosis in which the psychic and vaso-motor functions are predominantly affected; but constant changes in the thyroid cannot be explained on this idea.

Möbius is the chief defender of the theory of hyperthyroidization, in which the thyroid forms the starting-point for all the symptoms. Certain authors have shown that unpleasant symptoms—flushing, tachycardia, etc.—may follow the excessive administration of thyroid extract in normal animals, and it has been conceived that in this disease the enlarged thyroid is in a state of great secretory activity, pouring into the lymphatics far more of its secretion than normal, and thus bringing about the characteristic symptoms. This view seems further supported by the results of surgical extirpation of part of the gland—the relief of the symptoms being frequent. Not all the symptoms can be produced by injection of thyroid extract into normal animals, however, nor can all of the symptoms of exophthalmic goitre be relieved by extirpation of the active gland. For example, the exophthalmos can neither be produced by thyroid extract nor always relieved by thyroidectomy. There is much in favor of this theory, but also several arguments opposed to it are difficult to answer. The disease is considered to be a sort of general antithesis to the condition of myxœdema, which we know to be due to loss of the thyroid, and hence again the idea that such a reversal of the symptoms of myxœdema must be due to hyperthyroidization. But his-

tologically we cannot say with certainty that the gland is secreting actively. Indeed, of the usual colloid we see little or nothing at all. The theory fails to explain several important symptoms. The results of the operation for extirpation of part of the gland are not uniformly good, and indeed not especially better than the rest in bed and regular régime alone; and finally cases of exophthalmic goitre in combination with myxœdema have been described—a condition which must directly contradict and disprove the theory of hyperthyroidization.

Ehrlich thinks that the enlargement of the thyroid, and indeed most of the other symptoms, are due to the arterial hyperæmia, but he fails to explain this itself.

Mendel's theory of a lesion in the corpora testiformia falls on account of the inconstancy of such a lesion.

Finally, a theory has been based upon the effect upon the eyes of stimulation of the cervical sympathetic, ascribing the exophthalmic goitre, or at least many of its symptoms, to a lesion of the sympathetic. Now it was stated above that lesions of the sympathetic are by no means constant or even common, but the theory is not plausible upon the face of it, for the following reasons: Section of the sympathetic causes pallor of that side of the face, retraction of the eye, and narrowing of the pupil, while stimulation causes a flushing of the face; sweating on that side, protrusion of the eyeball, widening of the palpebral fissure, and dilatation of the pupil. Those symptoms of exophthalmic goitre might therefore correspond with the results of a constant stimulation of the sympathetic, but even then the pupillary disturbances are absent in exophthalmic goitre, while they form the most striking consequence of stimulation of the nerve.

The nature of the exophthalmos has given rise to much discussion in this connection. It is by no means proven that it is due to distention of retrobulbar vessels; nor can it be shown that it is due to stimulation of the sympathetic, perhaps by pressure of the enlarged thyroid, for removal of the goitre influences it very little. Protrusion of the eyeball is, however, not impossible to the normal individual, and experiments of Filehne¹³ and Durdafi¹⁴ have shown that irritation of the corpus testiforme will produce exophthalmos even after the sympathetic is cut through. So also Kotschanowski¹⁵ claims that it may be produced by stimulation of certain anteriorly placed cortical centres. Either venous congestion in the orbit or sympathetic stimulation with its effect upon Müller's muscle may produce the exophthalmos,¹⁶ but it seems that there is less evidence for its production by the accumulation of fat in the orbit.

The theory of sympathetic irritation, being as it is without anatomical basis, explains only haltingly a few of the symptoms. It is impossible to make the lack of pupillary change agree with this conception, and the general tremors, general sweating, and vaso-motor disturbances, as well as the metabolic disorders and psychical symptoms, are not explained at all by such a theory.

None of the theories is entirely satisfactory in explaining the phenomena of the disease, but in all cases there is a characteristic alteration of the thyroid and to a less extent of the lymphoid structures, and aside from this the changes seem to be such as might be ascribed to a toxic substance. The question remains as to what was the primary cause of the change in the thyroid and whether the appearance of the toxic symptoms depends upon this change. The change is anatomically that seen in compensatory hypertrophy, but it is difficult to understand why such hypertrophy should arise and proceed to excess. It seems possible that the cause may be some infection which sets up a non-suppurative thyroiditis destroying many of the cells and leaving scars throughout the gland, after which the remainder becomes hypertrophied and its activities perverted; but it is hard to comprehend that such a compensatory regeneration should so overstep the normal as to produce results harmful to the organism.¹⁷

COURSE OF THE DISEASE; PROGNOSIS; TREATMENT.—The disease runs sometimes a very rapid course, terminating fatally after an illness of a few days only. In most instances it drags on for years and may end in recovery. The prognosis indeed is by no means very unfavorable, and a considerable proportion of the cases get quite well. There have been cases reported in which some sudden emotional shock is followed by intense symptoms, such as have been described, which after a short time disappear completely. In the cases in which the most intense symptoms are developed, however, and in which the clinical picture is complete, recovery without surgical interference is rare. The greatest variety of procedures has been employed in the attempt to cure these cases. From the medical point of view none are very satisfactory. Rest in bed, freedom from emotional disturbances, and the regular régime of the hospital seem to afford great relief in many cases, and are extremely important in the cure. The tachycardia is apparently not influenced by digitalis, although strophanthus is said to have some effect. Ergot and belladonna have been warmly recommended by some authors, and may do some good. Electricity, too, applied to the spine and peripheral nerves has been advocated by Erb and others.

Based on the remarkable results obtained by the administration of the thyroid gland in myxœdema numerous cases of exophthalmic goitre have also been treated in this way regardless of the theory of hyperthyroidization, but the effects have been either actually harmful or entirely negative. The cases in which thyroid therapy has produced untoward results have therefore been brought forward as a strong support of the idea that the thyroid is already secreting too profusely, and thereby causing the symptoms.

From the fact that the thymus is usually found enlarged in exophthalmic goitre extracts of thymus have been given in these cases, sometimes with remarkable temporary results, but without any permanent advantage to the patient. In the case referred to above, which occurred in the Johns Hopkins Hospital, administration of the thymus extract reduced the pulse rate at once from 200 per minute to normal. When it was discontinued the pulse rose again to 200, and was again brought to normal by the thymus extract. After a time, however, its effect disappeared, and the pulse rate remained high until the death of the patient. In another case there occurred a remarkable reduction in the size of the goitre during its use. Since the parathyroid lies embedded in the thymus in the ox and certain other animals, it seems possible that it may be included in the extract manufactured from the thymus of these animals and may be responsible for the above results.

Quite recently Lanz,¹⁸ Möbius,¹⁹ Goebel,²⁰ Schultes,²¹ and others have proposed and carried out a treatment which is based on other principles, and which they claim to be very successful. On the idea that the thyroid is concerned in the neutralization of poisons produced elsewhere in the body, and that in exophthalmic goitre it is so active that not only does it neutralize these poisons but further poisons the organism by the excess of this antitoxin (?), these authors attempt to supply this overactive thyroid with poison for neutralization by injecting the serum of thyroidectomized sheep, in which supposedly much of the poison must have accumulated, or by feeding them on the milk of such thyroidectomized animals. The chances for fundamental error in the conception of this treatment seem very great, for it is by no means proven that in exophthalmic goitre the thyroid is overactive; nor, on the other hand, is it proven that the function of the thyroid lies in the neutralization of poisons elaborated elsewhere.

In recent years the surgical treatment of exophthalmic goitre has become very prominent. It also is based upon the idea that the enlarged thyroid is overactive in pouring its secretion into the lymphatics, and the cases are therefore subjected to the partial extirpation of the thyroid.

The operation is a serious one, hemorrhage being very

difficult to control. The patients do not take the anæsthetic well and many have died on the table.

Of late years, however, many of these operations have been performed under a local anæsthetic. Kocher²² has reported fifty-nine cases, in which the results have been on the whole very satisfactory, often with almost complete or complete relief of all the symptoms. Usually the exophthalmos persists or disappears gradually, and often the improvement in the symptoms does not immediately follow the operation, but appears later. Much anxiety has been expressed from time to time as to the dangers of allowing the escape of thyroid secretion into the wound during such an operation, and the fever which sometimes follows the operations has been ascribed to this. Lanz,¹³ however, has shown experimentally that the most violent crushing and laceration of the thyroid which is then left *in situ* is not usually followed by any rise in temperature nor by any special untoward symptoms.

Ehrlich has reported eight cases of operative extirpation of part of the thyroid in exophthalmic goitre, but is far less enthusiastic about the results. Many of these were not relieved, or suffered a recurrence of all the old symptoms after a temporary relief. He thinks that on the whole the good results are due mainly to the regular régime of the hospital for a time after the operation and to the suggestive effect of the operation.

In some instances merely ligation of the vessels of the thyroid has been performed, often with favorable results.

Halsted at the Johns Hopkins Hospital has operated upon a large series of cases with very satisfactory results, although, in spite of the usual amelioration of symptoms, a complete cure seems not to be achieved in a considerable proportion of the cases. He has described with especial care the operative precautions necessary to avoid the destruction of the parathyroid glands and the resulting tetany.²³

Operations for the section or removal of the cervical sympathetic trunks have been performed (Jaboulay,²⁴ Balacescu²⁵), with results which they claim to be quite as good as those obtained by the extirpation of the thyroid.

Recently another method of treatment has been inaugurated by Rogers and Beebe of New York,²⁶ consisting in the administration of a serum prepared by immunizing rabbits by repeated injections of the thyroid substance from normal individuals or from cases of exophthalmic goitre. The serum of these rabbits is said to have the property of greatly improving the condition of the patient or even of curing the disease—a property possibly dependent upon its cytolytic activities which reduce the bulk of the thyroid. Some remarkable results are reported from the method of treatment.

A definite opinion as to the value of these different methods of treatment must, however, be reserved until our knowledge of the results is more extended.

William G. MacCallum.

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² Felix: Le Myxœdème Associé à la maladie de Basedow. Thèse de Paris, 1896.

³ F. Müller: Beiträge zur Kenntniss der Basedow'schen Krankheit. Deutsch. Arch. f. klin. Med., Bd. 51, 1893.

⁴ J. Donath: Beiträge zur Pathologie u. Therapie der Basedow'schen Krankheit. Zeitsch. f. klin. Med., Bd. 48, 1903.

⁵ B. Spiethoff: Blutdruckmessungen bei Morbus Basedowii. Centralbl. f. innere Medicin, 1902, No. 34.

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⁷ von Schrotter: Zur Symptomcomplex des Morbus Basedowii. Zeitsch. f. klin. Med., Bd. 48, 1903.

⁸ Mendel: Path. Anat. d. Morbus Basedowii. Deutsch. med. Woch., 1892, p. 89.

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¹² Farnet: Pathologische Anatomie des Morbus Basedowii. Virch. Arch., 143, 1896.

¹³ Filehne: Sitzungsberichte der phys.-med. Societät zu Erlangen, 14 Juli, 1878.

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¹⁶ Moussu: Thèse de Paris, 1896-97.

¹⁷ MacCallum and Cornell: On the Mechanism of Enophthalmos. Medical News.

¹⁸ MacCallum: Pathology of Exophthalmic Goitre. Jour. Amer. Med. Assoc., Oct. 5th, 1907.

¹⁹ Möbius: Neurol. Centralbl., 1901, No. 22.

²⁰ Lanz: Schilddrüsenfieber u. Schilddrüsenintoxikation. Mitth. aus. d. Grenzgebiet. d. Med. u. Chirurg., Bd. 8, 1901.

²¹ Goebel: Münch. med. Woch., 1902, xlix., 835.

²² Schultes: Ibid.

²³ Kocher: Morbus Basedowii. Mitth. a. d. Grenzgebiet. d. Med. u. Chirurg., Bd. ix., 1902.

²⁴ Halsted: Annals of Surgery, xlvii., No. 4, 1907.

²⁵ Jaboulay: Lyon Méd., 1896, lxxxi., 150.

²⁶ Balacescu: Arch. f. klin. Chir., Bd. 62, p. 59.

²⁷ Rogers: Jour. Am. Med. Assoc., xlvii., 1906; xlvii., 1907.

EYEBALL, ENUCLEATION AND EVISCERATION OF.—I. ENUCLEATION.—By enucleation is meant a shelling of the eyeball out of Tenon's capsule with preservation of the relation between the conjunctiva, ocular tendons, and the other contents of the orbit.

History.—In 1841 Bonnet, of Lyons, first described and recommended true enucleation. The operation had been performed in a very crude manner by Bartisch, of Saxony, in 1583, by passing a sharp spoon behind the eyeball and thus gouging it out of Tenon's capsule.

Bonnet's operation had the great merit of preserving the capsule of Tenon and disturbing as little as possible the soft parts of the orbit. It became justly popular. Like most surgical procedures it has been variously modified by different operators. During the past few years it has been greatly improved and its cosmetic effect enhanced by suturing the tendons of the four straight muscles to the conjunctiva.

Operation.—The following instruments are required: A stop speculum, fixation forceps, toothed forceps, strabismus scissors, strabismus hook, a strong pair of scissors curved on the flat for cutting the optic nerve, a needle-holder, fine curved needles, and black silk for sutures. A general anæsthetic is advisable, although the operation may be performed under local anæsthesia.

The lids being held apart with a stop speculum, the surgeon incises, with strabismus scissors, the conjunctiva and adjacent fascia all around as close as possible to the corneal margin, and dissects the same from the sclerotic as far as the insertions of the tendons of the straight muscles. The tendon of each straight muscle, beginning with the internal rectus, is then, in succession, raised upon a strabismus hook and secured with a suture of black silk, after which the tendon is severed with strabismus scissors as close to the eyeball as possible. The anterior portion of the eyeball being now free from all attachments, may be dislocated forward by pressing the stop speculum back. The curved enucleation scissors are next introduced with the points closed and are pushed backward between the eyeball and the detached conjunctiva until the optic nerve is felt. After the exact position of the optic nerve is found, it is included between the blades and cut close to the sclerotic by one strong cut. The eyeball now readily protrudes and is held by the fingers of the left hand, while the tendons of the two oblique muscles and all adherent tissue are severed close to the globe. A small ball of sterilized gauze is inserted in the capsule of Tenon for the purpose of checking hemorrhage and of aiding the next step, the suturing of the tendons of the straight muscles to prevent their retraction. Each rectus tendon is now drawn forward and fastened to the margin of the conjunctiva by the same suture which was inserted just before the division of the tendon. The sterile gauze should now be removed, the margins of the conjunctiva and capsule of Tenon united with several interrupted sutures, and a dry antiseptic dressing applied. Both eyes should be bandaged for twenty-four hours and the patient kept in bed for a couple of days. The socket should be washed out once daily with physiologic salt solution until after four or five days, when all dressings may be discontinued.

The technique of the operation, as above described, has been varied by different operators. The most impor-

tant variations relate to methods of preparing the stump after enucleation, which will best secure motility of the prosthesis and furnish cosmetic results. The following method has been brought forward by G. F. Suker: After removing the eye, the severed tendons of the recti muscles are brought together by means of the silk guides and sutured one to the other with either catgut or silk. The conjunctiva from above and below is then brought over the muscle stump and sutured with a continuous or interrupted suture. H. V. Wurdemann, who was one of the first ophthalmologists to point out the advantages of a properly prepared stump, makes a pouch suture by weaving the needle along the cut edges of the divided conjunctiva and Tenon's capsule. In passing the recti tendons, each one is picked up on the needle.

H. Schmidt has suggested the following method: Each tendon of the recti muscles is secured by a catgut suture, and, after division, is fastened to a slit made in the conjunctiva over the site of the tendon's insertion. The opposite edges of the conjunctiva are then brought together with a continuous suture.

Priestley Smith has described the following method of suturing the tendons to the conjunctiva: A narrow horizontal fold of the conjunctiva over the internal rectus is pinched up so as to include the subjacent connective tissue and muscle, and a black silk thread is carried through these structures by means of a curved needle. The suture is then tied firmly but not too tightly. A second suture is applied in like manner to the external rectus. The upper and lower recti may be treated in the same way, but this is of less importance. The enucleation is then carried out and the conjunctival aperture may or may not be closed by one or more vertical sutures.

Complications and Accidents.—Hemorrhage, occasionally severe and persistent, may occur during the operation or later. In enucleating an inflamed eye, there is always a good deal of hemorrhage, particularly where there has been extension of inflammation into the surrounding tissue. The hemorrhage in this case is beneficial. Hemorrhages following an enucleation may require repeated packing of the orbit with antiseptic gauze. Occasionally a secondary hemorrhage occurs, when the dressings must be removed and the orbit packed with gauze. In these cases the tissues of the orbit may become greatly swollen from infiltration with blood. In chronically inflamed eyes, dense adhesions, binding the conjunctiva and its underlying fascia to the sclerotic and the tendons of the straight muscles, may be encountered. These cases often require a most careful dissection in order to expose the tendons, but by taking time and keeping the sclerotic always before him, the surgeon may perform the operation without accident. In enucleating an eyeball that has been perforated, or one soft from any cause, great care must be taken to remove it without leaving portions of the sclera and choroid behind. When an eyeball is enucleated because it contains a malignant growth, the posterior orbit should be carefully explored with the finger and probe before severing the optic nerve; and if a tumor is found, it should be removed along with the eyeball. As much of the optic nerve as possible should be removed with the globe. In very rare cases, enucleation has been followed by fatal meningitis, especially when performed on an eye within which suppuration was taking place. Up to 1900 G. E. de Schweinitz had collected fifty-two cases of fatal meningitis following enucleation, "thirty-three of which certainly—and a larger number probably—had followed enucleation for one stage or another of suppurative disease within the globe." The risk of a fatal termination from any cause after enucleation is about one in sixteen hundred. Meningitis after enucleation of a non-suppurating eyeball is exceedingly rare. In 1898 the Committee of the Ophthalmological Society of the United Kingdom could not find a single instance among 10,734 cases gathered from various sources.

Indications for Enucleation.—There are certain affections of the eye for the relief of which enucleation is demanded and cannot be replaced by any other operation.

Enucleation is demanded in all cases of malignant tumor of the globe except in those rare cases of tumors which grow at the limbus and on the conjunctiva or iris. It is also required in cases of malignant tumors of the orbit which cannot be removed without sacrificing the eye. Enucleation is to be performed in those cases of sympathetic ophthalmitis in which the sight of the exciting eye has been lost. It is also demanded in the cases of eyes so injured that they are likely to excite sympathetic ophthalmitis, if two weeks or more have elapsed since the injury; for while enucleation cannot prevent all cases of sympathetic ophthalmitis, it is the operation which holds out the best chance for the prevention of the disease.

On this account enucleation should be performed in the case of an eye with a wound so situated as to involve the ciliary region, and so extensive as to have destroyed the sight or to make its ultimate destruction by iridocyclitis reasonably certain. It is also indicated in the case of an eye with a wound in the ciliary region, complicated by severe inflammation of the iris or ciliary body, even if sight is not destroyed; or of an eye containing a foreign body, which judicious efforts have failed to extract, and in which severe iritis is present, even if sight is not destroyed. Enucleation is also to be performed in the case of an eye in which the wound has involved the cornea, iris, or ciliary region, and in which persistent sympathetic irritation in the fellow-eye has occurred, or in which there have been repeated relapses of sympathetic irritation; in the case of an eye long blind from injury which has become red and painful; in cases of painful phthisis bulbi, and in those in which the choroid has undergone calcareous changes. Enucleation is also indicated in cases of grave traumatism in which the sclerotic coat is extensively lacerated.

Other affections, believed by many surgeons to require enucleation, but for which one of its substitutes may be performed, are: Eyes so injured that they are likely to excite inflammation, which have come under observation within two weeks from the time of injury; painful glaucomatous eyes, unrelieved by sclerotomy; chronic painful iridocyclitis; panophthalmitis without involvement of the orbital tissues. In extreme old age enucleation is to be preferred on account of the recovery being smoother and shorter than is usually the case in evisceration. The same consideration may decide both the surgeon and the patient in favor of enucleation in the case of a working-man, especially where the cosmetic results are not important.

The Relation of Simple Enucleation to the Wearing of an Artificial Eye.—The artificial eye may be fitted as soon as the wound is entirely healed, in the second or third week. The following rules have been adopted by the Moorfield Ophthalmic Hospital, London, for the guidance of patients wearing artificial eyes:

To put the eye in: Place the left hand flat upon the forehead, and with the two middle fingers raise the upper lid toward the eyebrow; then, with the right hand, push the upper edge of the artificial eye beneath the upper lid, which may be allowed to drop upon the eye. The eye must then be supported with the middle fingers of the left hand while the lower eyelid is raised over its lower edge with the right hand.

To take the eye out: The lower lid must be drawn downward with the middle finger of the left hand; and then, with the right hand, the end of a small pin must be put beneath the lower edge of the artificial eye, which must be raised gently forward over the lower lid when it will readily drop out.

Patients very soon become expert in introducing or taking out artificial eyes and do not require the aid of a pin in removing them. The artificial eye must be removed every night and carefully cleansed. In selecting an artificial eye for use after enucleation the various forms of glass eye, proposed by Snellen, are decidedly superior to the older form of a simple shell. The cosmetic effect of the Snellen reformed eye after a well-performed enucleation is so good that many surgeons believe

that it renders unnecessary the operations which have been brought forward as substitutes for enucleation.

IMPLANTATION OF AN ARTIFICIAL GLOBE IN TENON'S CAPSULE AFTER ENUCLEATION (FROST-LANG OPERATION).—The eyeball is enucleated in the ordinary manner, and after all hemorrhage has been arrested an artificial sphere is inserted within Tenon's capsule for the purpose of forming a more prominent stump and giving it greater activity and mobility. Glass and gold spheres are commonly employed, more rarely celluloid or silver balls. Sterilized paraffin injected into Tenon's capsule has been advocated by Ramsay and Oatman. The capsule and conjunctiva are sutured over the artificial ball with silk sutures, the tendons of the straight muscles having first been secured in the manner described under enucleation. The following method of performing the operation has been introduced by C. A. Oliver: "The conjunctiva around the entire corneal limbus is freed from the globe and dissected sufficiently far back so as to expose the tendons of the four recti muscles. The tendinous extremities of the muscles are made ready for separation from the globe. A half-curved needle with its point directed toward the corneal border and holding a long piece of catgut thread is carried directly through the belly of the internal or the external rectus muscle and brought out of the tendon of the muscle just behind the remaining attachment to the globe. The muscle thus secured is cut loose from the globe just as in ordinary tenotomy. The catgut thread is drawn through as far as practicable, and a sufficient length of the strand of gut is left untouched to allow a loop broad enough for free manipulation between it and the eyeball. The needle is carried over to the opposite side of the cornea, and with its point directed away from the cornea is made to transfix the tendinous belly of the other lateral muscle, which is secured and freed from its attachment to the eyeball. The vertically placed muscles are dealt with in a similar manner. The four recti muscles are thus freed from their attachments to the globe, and each pair of muscles secured by a loose sling, that can be tied the moment this becomes necessary. Working in between the broad loops of catgut, attached to the ends of the muscles that are held apart by an assistant, the eyeball is enucleated. The cavity previously occupied by the globe is thoroughly cleansed and a water-tight glass ball, about three-fourths the size of the normal eye, is dropped into place. The ends of the lateral recti muscles, which are held by the lower and first-placed thread, are neatly trimmed and sutured together. The same is done with the two ends of the vertical straight muscles. The circular opening made by the cut edges of the conjunctiva is made into a lozenge by a couple of horizontal snips, and is carefully brought into linear apposition by a series of silk threads. The operative field is covered by a gauze protective bandage upon which ice compresses are placed."

Indications and Contraindications.—An artificial globe may be implanted in Tenon's capsule whenever it is necessary to remove the eyeball completely, except in cases of malignant disease, sympathetic ophthalmitis, suppuration within the globe, and in extreme old age.

Complications.—These are: Hemorrhage, orbital cellulitis, sympathetic irritation, tearing out of the stitches from sloughing with escape of the artificial ball, and late cicatricial contraction of the orbital tissues, causing extrusion of the ball. Adolph Brunner has lately advocated the insertion of a glass ball with a hole through the middle, which is covered in with glass so as to keep the ball air- and water-tight. By a somewhat elaborate method of stitches, this is held in, and he claims is less liable to be thrown off than a simple globe.

After-Treatment.—The eye should be dressed with a dry antiseptic dressing and both eyes bandaged. Care should be taken to avoid using pressure bandages. If much reaction follows, it is advisable to employ an ice bag for the first twenty-four hours. The patient should be confined to bed for four or five days.

An artificial shell—the ordinary or Snellen's—can be

inserted at the expiration of a month or six weeks. The cosmetic result is apparently no better than that which is obtained by a properly performed enucleation and the wearing of a Snellen reformed eye.

Implantation of a Piece of Sponge in the Orbit after Enucleation.—This procedure has been suggested by Claiborne, of New York, and Belt, of Washington, for the purpose of gaining a more prominent stump and an improvement in adapting prosthesis. The method has never come into general use on account of the prolonged convalescence and the late results being no better than those of a well-performed enucleation.

II. EVISCERATION.—In this operation the cornea and entire contents of the eyeball are removed, the sclera alone remaining. This procedure was first proposed by Alfred Graefe, in 1884, to prevent meningitis after the removal of eyes affected with panophthalmitis.

The instruments required are eye speculum, fixation forceps, a Graefe or Beer knife, strabismus scissors, sharp spoon, needle-holder, small curved needles, catgut and silk sutures.

Operation.—After general anaesthesia the speculum is introduced and the eyeball steadied by grasping with fixation forceps a fold of conjunctiva near the corneal margin. The eye is then transfixed just back of the corneal limbus with a Beer or Graefe cataract knife, which is made to cut its way out at the upper or lower sclero-corneal border, so as to include the corneal and about 1 mm. of the scleral margin in the flap. The flap is now grasped with forceps and the remainder of the incision completed with scissors. The next step is to remove the entire contents of the sclera, great care being taken that nothing is left behind, especially none of the choroidal tissue. The wound being kept open by two pairs of forceps, a sharp spoon-shaped instrument, grasping its edges about 10 mm. apart, is pushed between the choroid and sclerotic and carried sideways and deeper in order to detach the whole contents of the sclerotic, if possible unbroken.

It is usually impossible to eviscerate the contents of the globe as a whole. They must be removed with gauze sponges grasped by forceps, which are given a rotary movement, until, by scraping and wiping, the inner surface of the sclera is made perfectly clean. After hemorrhage has been controlled, the cavity should be irrigated with physiologic salt solution and the edges of the sclera and conjunctiva brought together by interrupted silk sutures. If preferred, the edges may be united by means of a suture similar to the gathering string which draws shut a tobacco pouch—a suture sometimes called the tobacco-pouch suture, or the purse-string suture.

Gifford, of Omaha, whose experience in evisceration has been unusually large, covering over one hundred cases, has devised the following method of operating: A large conjunctival flap is first turned back and a long meridional incision made through the sclera. Evisceration is performed through this opening, leaving the cornea intact. Gifford claims that the reaction is less and the stump better than when the cornea is excised. The latter shrinks to a mere patch on the anterior surface of the stump.

The dressing after evisceration should be a light, dry, antiseptic one. The patient should remain in bed at least four or five days with both eyes bandaged. Cold applications should be used for a day or two to keep down the reaction. The sutures may be removed in from three to four days. The recovery is commonly less smooth than that from simple enucleation, and considerable pain with cedema and swelling of the surrounding tissues may follow the operation. The operation is often performed when the inflammatory process is already high, and when the orbital tissues are secondarily involved. No cases of meningitis have occurred. Sloughing of the sclera has been noted, and a painful stump may be one of the complications.

Indications for Evisceration.—The operation having been introduced by Alfred Graefe as a substitute for enucleation in cases of panophthalmitis, it very naturally

followed that this affection at once took front rank as an indication for evisceration. Graefe had lost two patients in 1863 from meningitis following enucleation, and almost all surgeons in Germany, where his influence was supreme, feared to enucleate an eye during the height of panophthalmitis. Mauthner tells us that this feeling went so far that a German operator even excused himself for having enucleated two panophthalmitic eyes with the best results, because he did not know at the time what Graefe had said on this point. Writing in 1878, Mauthner graphically describes his own feelings on the subject. "Personally," he says, "I stand in awe of Graefe's advice never to operate if the panophthalmitis is distinctly pronounced. I have never enucleated an eye under such circumstances, and I doubt if I shall ever make up my mind to do so. The terrible apparition in von Graefe's cases impresses me so deeply that at the very sight of an eye in a state of panophthalmitis, and the thought of enucleating it, the dread of a fatal result is conjured up before me."

Notwithstanding his fears, Mauthner apparently had very grave doubts regarding the justifiability of abstaining from operation, and allowing suppuration within the eyeball to continue without interference. Meantime, the English oculists, under the leadership of Critchett, continued to enucleate during panophthalmitis as complacently as though Graefe had never warned against it, and Gunn, discussing a fatal case reported by Nettleship in 1886, said that this was the first fatal occurrence among over a thousand enucleations done at Moorfield Ophthalmic Hospital. American ophthalmologists have never paid much attention to panophthalmitis as a contraindication for enucleation, and Noyes, in a paper read before the American Ophthalmological Society in 1889, on "Enucleation during Panophthalmitis," says: "We are certainly justified in performing the operation notwithstanding the warnings and alarming declarations of Prof. Alfred Graefe."

Although the risk of a fatal termination after enucleation during panophthalmitis is so small that the operation may be performed almost with impunity, there can be no doubt that when the purulent inflammation has extended to the orbital tissues evisceration is the safer plan. Staphylococci of the cornea, especially when they occur in children, are well suited to evisceration. Painful, blind, glaucomatous eyes, or eyes blind from chronic, non-traumatic iridocyclitis, may also be safely eviscerated. This operation will also be indicated in the cases of eyes injured in the anterior portion of the globe, when all thought of recovery under conservative treatment has been abandoned within two weeks of the time of injury.

Contraindications.—These are malignant disease, sympathetic inflammation, sympathetic irritation, phthisis bulbi, ossified choroid, and foreign bodies penetrating the orbit.

The Relation of Simple Evisceration to the Wearing of an Artificial Eye.—A Snellen artificial eye may be inserted during the third or fourth week. The ultimate cosmetic effect is no better than, and in some cases not so good as, that obtained after enucleation performed according to modern technique.

EVISCEATION OF THE EYEBALL, WITH INSERTION OF AN ARTIFICIAL VITREOUS; MULES' OPERATION.—Mr. Mules, of Manchester, England, in 1886, modified the operation of simple evisceration by the introduction of a glass ball into the cavity of the sclera. The operation is performed as follows: After general anesthesia a stop speculum is introduced and the conjunctiva freed all around from the corneal margin and dissected back as far as the equator of the eyeball, without disturbing the relations of the muscles. The cornea and 1 mm. of the scleral margin are then removed in the manner described under evisceration. A triangular portion of the sclera, above and below, should also be removed to facilitate the introduction of the artificial vitreous, and in order that the coaptation of scleral edges over the same may be perfect. Next, the contents of the globe should be

removed in the manner described under simple evisceration, and all hemorrhage arrested by packing the scleral cavity with dry sterile gauze, or gauze soaked in hot sterile water. The next step is the introduction of a thoroughly sterilized artificial vitreous, usually of glass or gold. A sphere of such size that it can be easily inserted within the scleral cavity is selected. The introduction of the sphere is best effected by means of a special instrument designed for the purpose by Mr. Mules. The margins of the scleral opening are then united vertically by means of interrupted silk sutures, and the conjunctival opening is closed by another line of sutures placed at right angles to the sclerotic line of closure. The greatest care must be observed to secure absolute asepsis during the operation and at all subsequent dressings. A bandage which does not make much pressure should be adjusted over a dry antiseptic dressing. The fellow-eye should also be bandaged and, unless for special indications, the dressing should not be removed for forty-eight hours. Should there be decided reaction, iced compresses should be applied. The patient should be kept in bed for three or four days and both eyes bandaged until there is firm union of the wound. The superficial sutures should be removed on the third day, the scleral suture remaining permanently.

Some surgeons perform the operation according to a different technique from that described above. Gifford eviscerates through a horizontal incision in the sclerotic according to his special method previously described, and implants the artificial globe through this opening without removing the cornea. Some operators close the sclerotic and conjunctival wounds with the same sutures.

The purse-string suture is used by some of the best operators for closing the scleral opening, after which the conjunctival wound is closed with another purse-string suture. Some operators advise the removal of the conjunctival suture at the end of forty-eight hours. Mr. Collins, of Moorfield Hospital, believes that many failures of this operation are due to allowing the superficial suture to remain too long.

Indications.—The chief indications for this operation, as given by de Schweinitz, are: Staphylococci of the cornea and sclera, ruptured or injured eyeballs when the sclera is not too much lacerated and when the accident is of recent date, absolute glaucoma, buphthalmos and non-traumatic iridocyclitis.

Contraindications.—The following contraindications are enumerated by the same authority: Suppuration of the eyeball; morbid growths; much shrunken eyeballs, the contents of which have undergone bony or calcareous change; sympathetic ophthalmitis; sympathetic irritation and pathologic conditions of the eyeball which are likely to produce either of the last-named affections; extensive injuries of the eyeball, with much bruising and laceration of the sclera; dacryocystitis and ocular conditions demanding enucleation or its equivalent in very old persons.

Accidents and Complications.—The operation may be followed by excessive reaction manifested by marked swelling of the lids and chemosis of the conjunctiva, headache, nausea and vomiting, and elevation of temperature. It is probably always caused by faulty technique, as imperfect asepsis, failure to arrest hemorrhage, the use of strong antiseptics and undue dragging upon the optic nerve. Sloughing of the sclera and consequent cutting out of the stitches occur in about eight per cent. of all cases. Extrusion of the artificial vitreous within the first week or at a much later period took place in seventeen per cent. of the three hundred and sixteen cases in the hands of thirty-three different operators, tabulated by de Schweinitz. The chief cause of escape of the artificial globe is failure of the edges of the scleral wound to unite. Another important cause of the throwing-out of the glass ball is that it may have been too large or too small for the scleral cup. An irritable and painful stump requiring removal has been met with as a complication following the operation. Sympathetic inflamma-

tion has been met with as an unfortunate complication in a number of instances. While in most cases it was due to the seeds of the disease having been planted before this operation was performed, it seems in several instances, as in the case reported by Carrow, to have been directly due to the operation itself. The report of the committee of the Ophthalmological Society of the United Kingdom in 1898 contains the following statements: "We have not found a record of any case of sympathetic ophthalmitis following evisceration without the implantation of an artificial globe, and we have collected records of five cases of sympathetic ophthalmitis after the operation of evisceration and the introduction of an artificial globe into the emptied sclerotic." Sympathetic irritation has been met with on rare occasions and required the removal of the stump.

Special Advantages with Relation to the Wearing of an Artificial Eye.—After a successful Mules' operation the motility of the stump and artificial eye is usually better than that after enucleation, the implantation of a ball in Tenon's capsule, or simple evisceration. The cosmetic result is extremely satisfactory, for the natural contour of the lids being preserved, there is none of the shrunken appearance so often presented by artificial eyes. The absence of accumulations of mucus and tears adds to the patient's comfort and satisfaction. The high percentage of failures, due to extrusion of the artificial vitreous, must be greatly reduced before the operation can take a permanent place in ophthalmic surgery. At the present time the prevalent feeling among ophthalmologists regarding the operation of Mules is one of disappointment.

Edmund W. Stevens.

FACIAL HEMIATROPHY.—(Synonyms: Unilateral atrophy of the face; Progressive facial hemiatrophy; Progressive laminar aplasia; Facial trophoneurosis; Facial circumscribed atrophy.)

The first known description of facial hemiatrophy is that by Parry, written in 1825. In the year 1846 Romberg described the condition more definitely and called it a trophoneurosis.

The disease consists of an acquired circumscribed atrophy of the face. The atrophy, involving soft tissues and bone, follows a chronic course, and finally becomes spontaneously stationary.

Something over one hundred authentic cases have been reported.

ETIOLOGY.—The disease belongs to the period of youth. Practically all of the reported cases began before the thirtieth year. Women are more frequently affected than men, in the proportion of about two to one. It does not appear that nationality, station in life, or heredity has any influence on the development of the syndrome. In the reported cases it has followed typhoid fever, measles, scarlet fever, syphilis, and other infectious diseases. It has been observed in the course of multiple sclerosis, syringomyelia, multiple exostoses of the face and head, scleroderma, insanity, epilepsy, and hysteria. It is not unusual for the patient to ascribe it to blows or other injuries to the face. In a number of cases the early symptoms have been those of a severe trigeminal neuralgia. In one case which I saw there had been a severe malarial infection one year before.

PATHOLOGICAL ANATOMY.—Various theories have been advanced in regard to the lesions which may produce facial hemiatrophy. Disease of the sympathetic nerves, of the peripheral distribution of the fifth cranial nerve, of the Gasserian ganglion, of the nuclei of the fifth nerve, and of the cortex of the cerebrum have in turn had their theoretical advocates. The principal anatomical evidence rests on the findings in Mendel's case; this was a woman who for fifteen years had suffered from left facial hemiatrophy. The autopsy showed the epidermis normal except for a moderate degree of thinning, the connective tissue was diminished, the blood-vessels were few and small, the fibres of the muscles were somewhat thinned without degeneration or nuclear

changes, and the facial nerve was normal. In the trigeminal the connective tissue around and penetrating the nerve was much thickened. In many places the number of nerve



FIG. 5151.—Facial Hemiatrophy Beginning in a Woman Twenty-four Years Old. (After Fromhold-Treu.)

fibres was diminished. Most of the changes were in the second division of the nerve. There was also atrophy of the descending root of the trigeminal and of the substantia ferruginea. Mendel believed that the facial atrophy was due to the proliferative interstitial neuritis of the trigeminal. In this case there was also an atrophy affecting the left upper extremity and some of the muscles of the shoulder and back. To account for this Mendel found an interstitial neuritis of the musculo-spiral nerve and a diminution in size and number of the cells of the anterior horn of the cord at the level of the fifth cervical nerve.

The antecedent neuralgias of the fifth nerve point to this as the site of the lesion. But how many severe neuralgias of this nerve have we not seen with no subsequent atrophy? Section of the posterior root of the trigeminal may be attended by unilateral atrophy of the muscles of the face, tongue, and bones of the face, and changes in the amount and color of the hair. Operations on the Gasserian ganglion have been said to be unattended by trophic changes in the skin.

Other autopsies in patients showing facial atrophy have shown other lesions which take them out of the group of cases now under discussion. Such was Graff's case, which showed on autopsy a progressive muscular atrophy, and that of Jolly and Recklinghausen, in which was found a disseminated sclerosis of the brain.

SYMPTOMS.—Patients who develop facial hemiatrophy usually present themselves to the physician complaining of a neuralgia in the distribution of the trigeminal nerve. After this has lasted for several weeks or months the cardinal symptom of the syndrome appears. This consists in an atrophy commencing in the skin of the face. There appears on the face a whitish spot which may soon be followed by other similar spots. These may extend until they cover half of the face, or may be limited to a small area. Gradually these areas change in color to a yellowish-brown, while the skin becomes thin and tightly stretched over the subcutaneous tissues. The extent of the atrophy may vary to a considerable degree. Fromhold-Treu indicates the varieties in his attempt to classify them: (a) Typical cases involving one-half of the face. (b) Incomplete cases involving a portion of one side of the face. (c) Double cases involving both sides of the face. (d) Cases in which other parts of the

same side of the body are involved. Following the atrophy of the skin there is a falling away of the underlying tissues. The fat may totally disappear, but at times is said to be replaced after the atrophic process has come to a standstill. The frontal, malar, upper and lower jaw bones may atrophy. The muscles supplied by the fifth nerve become very thin, but their electrical reactions remain normal and their function is not wholly destroyed, though much weakened. The nasal cartilages usually waste; less frequently the auricle is involved. The hair of the head, eyebrow, and beard may change color, become thin, or fall out altogether on the affected side. The glands of the skin are usually unaffected, but anidrosis has been noted as well as diminished lachrymal secretion. The blood-vessels may show through the attenuated skin, marking it with an underlying network. The tongue and gums are frequently atrophied on the affected side. The tightening of the skin may interfere with the movements of the jaw. In the one case which I have observed the mouth was drawn to the normal side by the overaction of the healthy muscles. Taste, touch, and the electrical reaction are usually normal, even in the wasted half of the tongue. The trigeminal pain is occasionally associated with spasmodic contractions of the muscles, or with fibrillary twitchings. As the atrophy advances the pain usually subsides. There may be paræsthesias or spots of hyperæsthesia (probably due to thinning of the skin). Anæsthesia and changes in the temperature sense are exceedingly rare. The muscles supplied by the seventh nerve are usually unaffected. Mills reports a case in which the hearing was affected, probably on account of an atrophy of the tympanum. The pupil may be contracted; or, as in Mailhouse's case, may be dilated and fail to react to light or accommodation. The eyeball on the affected side appears prominent on account of the atrophy of the surrounding tissues.

COURSE AND PROGNOSIS.—The disease is insidious in its origin and slow in its development. It may continue to advance for two or three years, but all the cases ter-

minate spontaneously, the majority at the end of one year, leaving an area of atrophy from which recovery is unknown. At the beginning one cannot predict the extent or duration of the atrophic process; it may involve a narrow furrow only, or half of the face, or even both sides of the face. As a rule a long and severe antecedent neuralgia suggests a less favorable prognosis. A cure or even an improvement in the atrophied parts is almost unknown, though some competent observers have claimed that in a few cases the face has filled out to a moderate

degree; this was probably due to an increase in the fat. To the patient, however, cessation of the pain and muscular cramps is an improvement.

DIAGNOSIS as a rule is not difficult. The points particularly to be borne in mind are that the disease is an acquired one, developing before the thirtieth year. There is a change in the color of the skin followed by atrophy; the muscles usually affected are those supplied by the fifth nerve. Congenital asymmetry and forms of degeneracy should be easily differentiated. Confusion in cases of hemiplegia and the malnutrition of sympathetic paralysis is hardly possible. In Bell's palsy the muscles supplied by the seventh nerve only are affected. In these muscles there is a reaction of degeneration to the electric current, and tissues other than muscular are not involved. In the type of progressive muscular atrophy which first involves the face, the muscles alone atrophy; the skin, connective tissue, and bone are not affected. This disease, moreover, is progressive, and later other parts of the body are involved. Atypical cases of scleroderma may be confounded with facial hemiatrophy. The skin of scleroderma is usually harsh and infiltrated, while that of facial hemiatrophy is thinned.

TREATMENT.—At the present time we know of no measure that will limit the course of the disease. Neuralgias following abscesses of the teeth, tonsillitis and the infectious diseases should receive careful attention. Electricity and massage appear to have no influence on the course of the disease or in restoring the atrophied tissues. No drugs which have been tried have been proved of benefit excepting in so far that they control the neuralgic pains and muscular spasm. Sachs suggests thyroid extract. The value of this, as far as I know, has not been demonstrated. Section of the trigeminus, on the theory that the nerve stimulus is perverted, should be considered. Various contrivances have been devised for correcting the resulting deformity. Sachs has used a pad or rubber plate in the mouth. Eckstein has improved the appearance with subcutaneous injections of paraffin.

T. Stuart Hart.

FACIAL HEMIHYPERTROPHY is a rare affection consisting of circumscribed enlargement of one side of the face. The process usually involves the skin, connective tissue, blood-vessels, muscles, and bone. In some cases the skin is harsh and rough, while the sebaceous glands are much hypertrophied and clogged with an abnormally thickened secretion of gummy consistence. The hair is often thick and coarse. In the case reported by Dana the bones were alone involved in the process; the soft tissues were not hypertrophied. The external ear may take part in the enlargement. Here either the cartilage alone or all the tissues may be involved. The hypertrophy may extend into the mouth implicating the gums, soft palate, and jaw. The hypertrophy may be limited to a part of the face on one side, or may extend somewhat across the median line.

But little is known of causes underlying the condition. Of the twenty-three cases collected by Sabrazès and Cabannes eighteen were congenital. In Schick's case the hypertrophy commenced in the second year with no known cause. In Berger's case there was an obstinate antecedent neuralgia of the fifth nerve. Montgomery's patient had brain fever when two years old. There was no neuralgia. When nine years of age the patient had an osteomyelitis of the left maxilla. About one year later hypertrophy first appeared in the gums of the left side. In Dana's case the patient was also affected with gigantism. It is probable that several distinct conditions have been described under the term of hemifacial hypertrophy. Among the theories advanced as to the etiology of the acquired cases may be mentioned irritation of the fifth nerve through its roots or the Gasserian ganglion, and chronic hyperæmia of vascular origin.

The enlargement may be first noticed in the bones, particularly about the orbit, giving the eyeball the appearance of being depressed in its socket. The bony



FIG. 5152.—Facial Hemiatrophy Following Pneumonia in a Woman Nineteen Years Old. (After Möbius.)

minate spontaneously, the majority at the end of one year, leaving an area of atrophy from which recovery is unknown. At the beginning one cannot predict the extent or duration of the atrophic process; it may involve a narrow furrow only, or half of the face, or even both sides of the face. As a rule a long and severe antecedent neuralgia suggests a less favorable prognosis. A cure or even an improvement in the atrophied parts is almost unknown, though some competent observers have claimed that in a few cases the face has filled out to a moderate

hypertrophy gradually extends until the entire side of the head is included. In other cases (*e.g.*, Montgomery's) the process may begin in the soft parts, and the gums,



FIG. 5153.—Facial Hemihypertrophy in a Child. (After Sabrazès and Cabannes.)

skin, sebaceous glands, hair, connective tissue, muscle, and the bones become later involved. The enlargement of the blood-vessels may cause a reddening of the skin. The flow of saliva may be considerably increased.

There are few conditions which could be confounded with hemifacial hypertrophy. It has been suggested that it might be mistaken for hemifacial atrophy of the other side of the face; but anything more than a cursory examination could not fail to disclose the differences.

We know of no cases in which the hypertrophied tissues have been replaced by normal ones; but after a progression covering a period of several years it is probable that the condition may become stationary.

Treatment thus far has proved unavailing, either in limiting the course of the disease or in reducing the hypertrophy.

T. Stuart Hart.

FATTY DEGENERATION.—The truth of Virchow's teaching that fatty degeneration is a process in which fat is formed from the albumin of the cell as the result of a splitting-up of the albumin molecule has been thrown into doubt by the chemical studies of recent years. Although the question of the formation of fat from albumin cannot be said to be absolutely settled, the majority of investigators do not favor such an origin for the fat occurring in the cells in the condition designated as fatty degeneration. On the other hand, they hold that such fat is in many cases only the permanent fat of the cells, which under normal conditions is not visible microscopically, but which under certain pathological influences becomes separated into visible droplets. Fatty degeneration is in some instances, therefore, a fatty metamorphosis due to a change in the chemico-physical structure of the cells whereby the invisible fat of the cells becomes visible. The fat content of the cells is not changed during this process. Rosenfeld, Kraus, and others have shown that the renal epithelium, which normally shows no fat microscopically, contains, nevertheless, about twenty per cent. of fat. In fatty degeneration of the kidney there is no increase in the per cent. of fat present in the cells, although fat appears in the form of visible droplets. A similar fat metamorphosis has been shown to occur in the aseptic autolysis of various tissues. In the case of organs containing no fat as such, the latter may be formed by the chemical splitting-up of the lecithin, cerebrin, and protagon that may be present in the cells.

In certain cases it seems very probable that the fat droplets of fatty degeneration are not formed from the

invisible permanent fat of the cells, but represent a fat brought to the injured cells by the blood or lymph in the form of free fat or soaps. No fat synthesis takes place, although the fat content of the cells is increased. Such a pathological taking-up of fat occurs in various intoxications, particularly phosphorus poisoning. The fat may be that taken into the body or it may come from the fat depots from which it is set free by the action of the injurious agent. Rosenfeld and others have shown that in dogs fed with mutton fat there occurs a deposit of mutton fat in the fat depots. When such dogs are poisoned with phosphorus or phloridzin there occurs a fatty degeneration of the liver with the appearance of mutton fat in the liver cells in addition to the dog-fat. Leick and Winckler found the same thing to be true of the heart muscle of such dogs.

It is impossible to say at the present time with certainty whether the fat present in given cells represents a physiological or a pathological condition. The best criteria for such a judgment are the amount of fat present and its occurrence in localized areas or foci. In the majority of cases, however, fatty degeneration presents a definite pathological picture and can be easily recognized microscopically. It bears always the character of a definite tissue injury. The appearance of visible fat droplets in tissues not containing them normally is to be regarded as the manifestation of a chemico-physical disturbance of the cell. Practically, then, the most important change in our conception of the process is the recent view of the source and origin of the fat concerned in the manifestation of the tissue injury. Although the fat may not come from the albumin of the cell, the character of the process still justifies the use of the old term fatty degeneration, although in a somewhat different sense.

Aldred Scott Warthin.

FŒTUS, DEVELOPMENT OF.—Our knowledge of the development of the fœtus was in an exceedingly fragmentary condition until Wilhelm His, the distinguished German anatomist, published twenty years ago his noteworthy "*Anatomie menschlicher Embryonen*."

Age.—In regard to the ages of embryos of the first two weeks much uncertainty exists. Length is not entirely reliable, owing to distortions and variability in size. In attempting to determine age from the last day of the last menstrual period as the date of conception, there is often the difficulty of inexact history. The following table indicates in a fairly accurate way the length and ages of embryos:

Age.	Length.	Age.	Length.
Two weeks	2 mm.	Three months	50 mm.
Three weeks	5 "	Four months	100 "
Four weeks	8 "	Five months	200 "
Five weeks	11-12 "	Six months	300 "
Six weeks	16 "	Seven months	370 "
Seven weeks	20 "	Eight months	425 "
Eight weeks	25 "	Nine months	500 "

According to Mall their ages in days corresponds to the formula $\sqrt{100 \times (\text{length in millimetres})}$ for all embryos from 1 to 100 mm. long. Multiply the length of the embryo from vertex to the breech in millimetres by one hundred, and extract the square root, and the result will be its age in days. In embryos from 100 to 220 mm. long from vertex to breech their length in millimetres equals their age in days. Fig. 5154 indicates the relative sizes during the first eight weeks.

There are but few good collections of embryos in the world; the one at Leipsic and the one at Baltimore are the most important.

In development it is convenient to distinguish the three stages suggested by His. The stage of the ovum embraces the first two weeks; the embryonal stage from the third to the fifth week, during which the principal organs are established; lastly the fetal stage.

The Ovum Stage.—There are no observations on normal ova of the first nine or ten days. It is evident

from the material of the latter part of the stage of the ovum that there is an early and precocious development of the chorion and villi.

The youngest known normal ovum was described by Peters in 1899. It is ten to eleven days old and consists of a vesicle $3 \times 1.5 \times 1.5$ mm. in size. A section through the entire ovum is seen in Fig. 5155. The vesicle is formed by the chorionic membrane, consisting of an outer layer of epithelial cells covered by numerous villi which are

present. From these at a later period various structures arise. From the epithelial layer develop the epidermis of the skin and its appendages, such as hairs, nails, sweat glands, etc., the central nervous system, and portions of the eye and ear, mouth and nose. From the middle or mesenchymal layer develop the skeletal, muscular, circulatory, and urogenital systems; and lastly from the inner or entodermal layer, which is here represented by the lining of the yolk sac, develop the alimentary tract (pharynx, œsophagus, stomach, and intestines), the trachea and lungs, liver and pancreas, and bladder.

The next important human ovum was described by Spee in 1896. It measures 7×5.5 mm. and the embryo within is 0.37 mm. in length. Its age is about eleven days. The chorion is covered with villi and lined with mesenchyme (see Fig. 5156). The embryo is attached at one side by a broad pedicle, the so-called belly stalk. The amniotic sac is small and is continuous with the epithelial plate of the embryo, as in the preceding ovum. The primitive streak is represented in this embryo by a slight groove along the centre of the epithelial plate. Mesenchyme separates the epithelial plate from the large

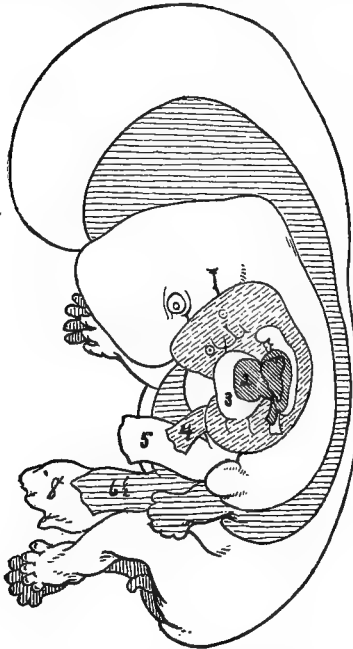


FIG. 5154. — Six Human Embryos taken from His' Standard Chart. Enlarged three times. The figures in the cut indicate the ages of the embryo in weeks. 2 is His' embryo S.R.; 3, embryo Lr.; 4, embryo A.; 5, embryo C'; 6½, embryo XCL.; 8, embryo Wt. (After Mail.)

in contact with the uterine wall of the mother, and an inner layer of mesenchyme. Attached to this inner layer at one side is the small embryo, but .19 mm. in length. It is apparently simple in structure, consisting of an epithelial plate facing the small amniotic cavity lined by flat epithelial cells, which are continuous with the epithelial cells of the plate. On the other side of the plate is a layer of mesenchyme, and projecting from this is the yolk sac lined by entodermal cells. The epithelial plate of the embryo, as well as the epithelium of the amnion, was probably at an earlier stage continuous with the epithelium of the chorion and the embryo, subsequently cut off after its sinking down or projecting into the vesicular cavity. One stage of such a process has been found in the monkey by Selenka. The projecting embryo is surrounded by mesenchyme continuous with that lining the chorion, as well as with that between the yolk sac and epithelial plate.

Already, then, in the youngest known ovum the so-called three primary germ layers are

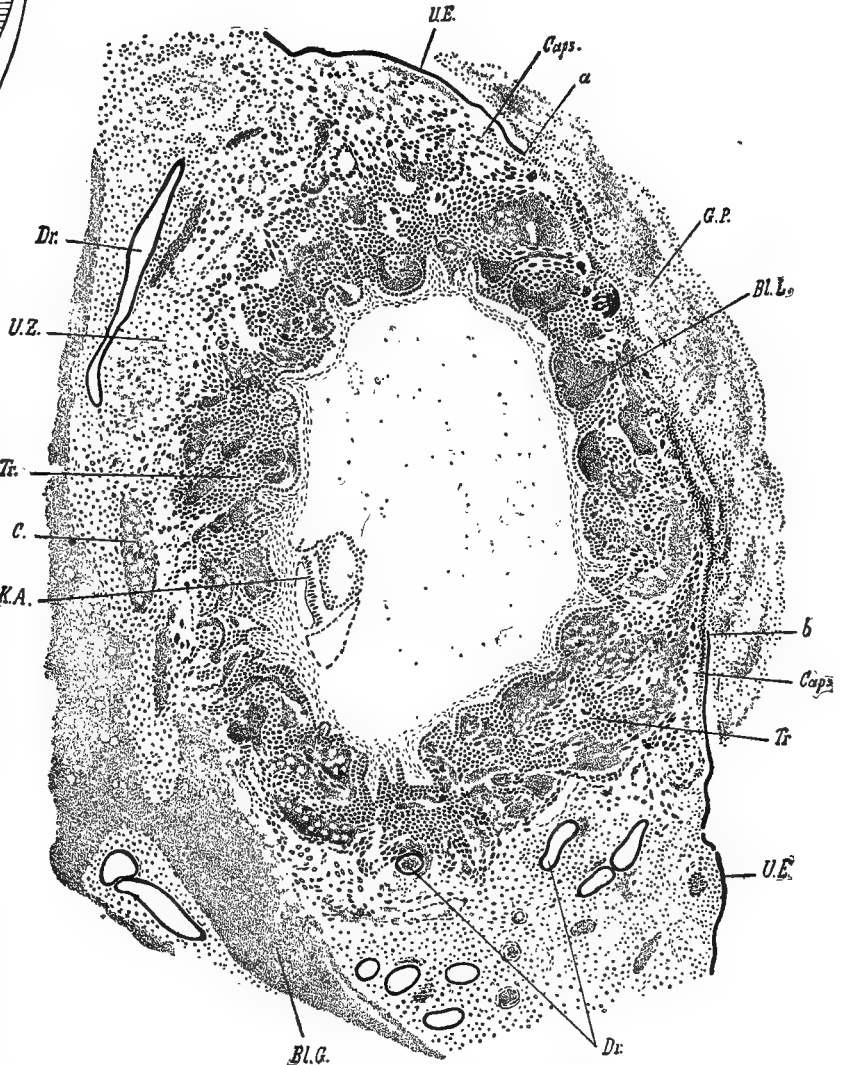


FIG. 5155. — Peters' Early Ovum. (Enlarged about 35 diameters.) U.E., Uterine epithelium; B.L.G., lakes of blood; Caps., decidua reflexa; G.P., "Gewebspilz"; Dr., uterine glands; U.Z., decidua vera; Tr., trophoblasts; C., capillaries; K.A., beginning embryo; B.L.G., large blood-vessels; a-b, point of entrance of ovum.

yolk sac, and a small diverticulum of the sac projects into the mesenchymal pedicle, constituting the first trace of the allantois. We thus see that the embryo in this

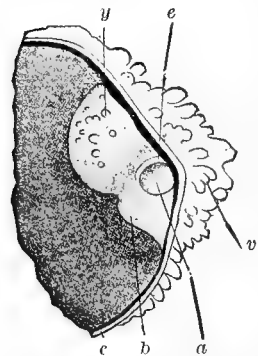


FIG. 5156.—Ovum Measuring 6×4.5 mm. (Enlarged about 10 diameters.) The left half of the chorion has been removed to show the embryo. *a*, Amniotic cavity; *b*, belly stalk; *c*, chorion; *e*, embryonic disc; *v*, chorionic villi; *y*, yolk-sac. (von Spee.)

either side of the median line. These are the so-called medullary folds and are the first traces of a differentiation for the central nervous system. The allantois as in the preceding embryo projects from the yolk sac into the pedicle or belly stalk.

Between this stage and the next one we shall consider, the embryonic plate changes from a flat discoidal structure to a somewhat cylindrical body by a bending ventrally of its lateral edges, to which the amnion is attached, thus gradually constricting the broad attachment of the yolk sac. At the same time the head and tail ends begin to project more and more, and the yolk sac is thus also constricted in an anterior posterior direction. Connecting pockets of the yolk sac remain at both the head and tail ends of the embryo to form the beginnings of the digestive tract. During this time the medullary folds have lengthened and grown toward each other, so as to meet in the mid-dorsal line, thereby enclosing a central canal, the beginning of the central canal of the spinal cord and the ventricles of the brain. In the next oldest ovum we are to consider, which was described by Eternod, there was an embryo 2.11 mm. in

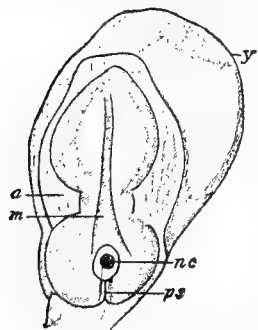


FIG. 5157.—Embryo 1.54 mm. in Length, from the Dorsal Surface. (Enlarged about 20 diameters.) *a*, Amnion; *m*, medullary groove; *nc*, neururetic canal; *ps*, primitive streak; *y*, yolk sac. (von Spee.)

become connected with the heart, and at its head end arises the ventral aorta dividing immediately into three pairs of branchial arches, which pass around the primitive foregut to unite beneath the medullary plate into the dorsal aorta.

From the dorsal aorta are given off the omphalo-mesenteric and the umbilical arteries. The first veins to develop are those which accompany the first formed

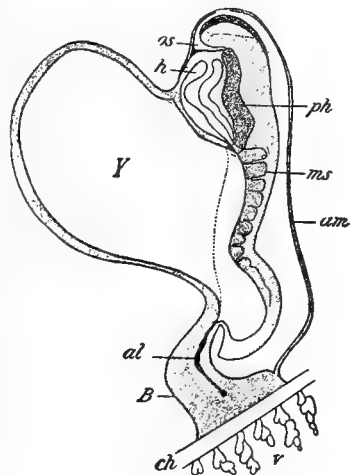


FIG. 5158.—Reconstruction of Embryo 2.11 mm. Long. (Enlarged about 25 diameters.) *al*, Allantois; *am*, amnion; *B*, belly stalk; *ch*, chorion; *h*, heart; *ms*, mesodermic somite; *os*, oral fossa; *ph*, pharynx; *v*, chorionic villi; *Y*, yolk-sac. (After Eternod.)

sus. The omphalo-mesenteric veins coming from the yolk sac and the umbilicals from the allantois join the sinus venosus at a slightly earlier date than do the Cuvierian ducts. At a later stage we shall see how this primitive arrangement is modified to form the adult condition. The yolk sac in this embryo is somewhat constricted along its attachment, leaving pockets of entoderm connected with it that lie in the head and tail

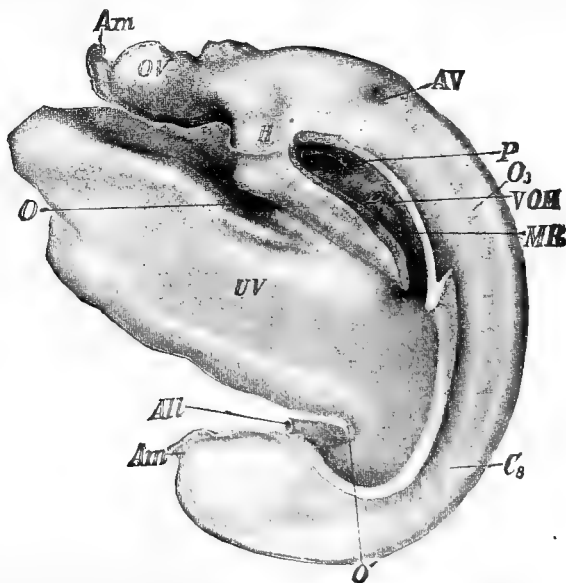


FIG. 5159.—Profile Reconstruction of the Embryo, 2.1 mm. Long. No. XII. $\times 37$ times. *Am*, Amnion; *OV*, optic vesicle; *AV*, auditory vesicle; *UV*, umbilical vesicle; *H*, heart; *VOM*, omphalo-mesenteric vein; *MR*, septum transversum; *O3*, third occipital myotome; *C8*, eighth cervical myotome. (After Mall.)

ends of the embryo. They form the primitive foregut and hindgut. At either side of the neural tube the mesenchyme has become differentiated into eight prim-

itive segments or myotomes, from which later much of the muscular system becomes differentiated.

A slightly older embryo, of about the same length, described by Mall, consists of an ovum measuring $18 \times 8 \times 8$ mm., and containing an embryo 2.1 mm. in length. The age is about two weeks (see Fig. 5159).

Many important changes have taken place. The embryo is connected to the chorion by a thinner stalk of mesenchyme containing the blood-vessels that carry on

the circulation between the embryo and chorion, the latter being in close contact with the uterine wall, and thus affording opportunity for nourishment and oxygen to pass from the mother through the thin walls of the villi, to supply the rapidly growing embryo with the essentials for growth and life. The embryo itself has greatly increased in length, and is curved into a semicircular form. The medullary plate is converted into a tube and the groove into its canal. At the anterior end of this tube are enlargements marking the beginnings of the brain. The remainder of the tube forms the spinal cord. The yolk sac, which is covered by blood-

vessels that communicate with those of the embryo, is more constricted and the fore- and hindguts are longer than in the preceding stage. From the foregut arises the pharynx with two gill pockets and a thyroid pocket. The neurenteric canal connects the hindgut with the central canal of the central nervous system. So while from the yolk sac are differentiating the two ends of the alimentary tract, the main portion is still embodied in the large sac. Near the origin of the foregut is a slight projection of the yolk sac for the beginning of the liver. In the anterior wall of the yolk sac, posteriorly to the mouth and beneath the pharynx, is the tubular heart. There are now fourteen pairs of mesenchymal segments or myotomes—three in the head, eight in the neck, and three in the thoracic region. The amnion at this period forms a small sac about the dorsal surface of the embryo.

The His embryo (Fig. 5161), as the normal curve of the medullary tube at this period is probably somewhat semicircular, as seen in Figs. 5159 and 5163. This so-called dorsal flexure, which is often pictured in text-books as a normal condition at this stage, I have been able to produce in pig embryos of a corresponding stage by rough handling while removing them from the uterus. Others from the same uterus, which were more carefully handled, do not show such a dorsal flexure, and we naturally conclude that similar treatment has produced a similar effect in the human embryo.

The His embryo Lg., 2.15 mm. long, contained in an ovum 15×12.5 mm., is the next important one to consider. Its age is about fourteen days. (Fig. 5161.) The forebrain has a marked ventral bend. Between the forebrain and the heart is now a well-marked invagination of the skin to form the mouth cavity. It is not as yet connected with the pharynx. Projecting from the forebrain are the optic vesicles, and farther back are invaginations of the ectoderm for the internal ear. Two gill clefts and three branchial arches are present, and branches of the aorta pass through the latter. The heart consists of a much bent tube.

The branchial arches and clefts are of great morphological importance, since they determine to a large extent the arrangement of the various organs of the head region. In the human embryo four clefts and five branchial arches appear on each side. The last arch is very indistinct. We thus see that during the first two weeks, which constitute the ovum stage, there has developed from the simple one-celled ovum or egg an embryo with its membranes, the amnion and chorion, the latter having over its entire surface numerous long branching villi, and in the embryo are already present the beginnings of the central nervous system, the alimentary tract, the circulatory system, the muscular and skeletal systems, the latter being represented by the chorda dorsalis, which has differentiated from the dorsal wall of the entodermal sac and canal. The primitive urogenital system has also begun to appear. The yolk sac remains throughout this stage the dominant feature of the embryo.

The Embryonal Stage.—During the third week the embryo grows rapidly in size and attains a length of about

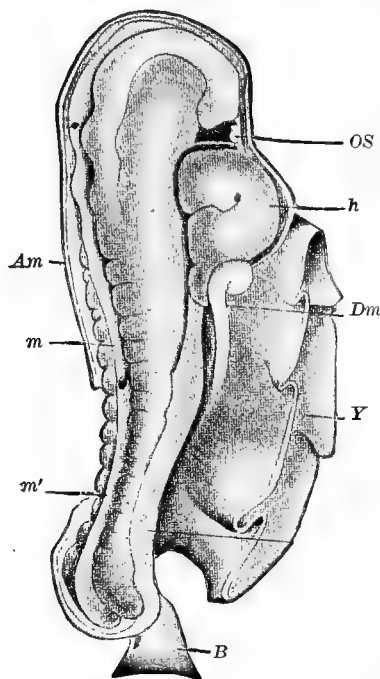


FIG. 5160.—Embryo 2.5 mm. Long. (Enlarged about 33 diameters.) Am, Amnion; B, belly stalk; h, heart; m, closed and m', still open portions of the medullary groove; Om, omphalo-mesenteric vein; OS, oral fossa; Y, yolk sac. (Kollmann.)

vessels that communicate with those of the embryo, is more constricted and the fore- and hindguts are longer than in the preceding stage. From the foregut arises the pharynx with two gill pockets and a thyroid pocket. The neurenteric canal connects the hindgut with the central canal of the central nervous system. So while from the yolk sac are differentiating the two ends of the alimentary tract, the main portion is still embodied in the large sac. Near the origin of the foregut is a slight projection of the yolk sac for the beginning of the liver. In the anterior wall of the yolk sac, posteriorly to the mouth and beneath the pharynx, is the tubular heart. There are now fourteen pairs of mesenchymal segments or myotomes—three in the head, eight in the neck, and three in the thoracic region. The amnion at this period forms a small sac about the dorsal surface of the embryo.

In an embryo described by Kollmann (Fig. 5160), and measuring 2.5 mm. in length, the edges of the medullary folds have come in contact throughout their entire length except for a short distance anteriorly, and thirteen pairs of mesodermic somites or myotomes are visible. The constriction of the yolk sac is even more pronounced than in the preceding embryo, and the hind end of the body has become defined, the belly stalk no longer seeming to be a posterior continuation of the body, but arises from the ventral surface. The oral fossa is more marked.

The general shape of this embryo is quite different from that of the preceding one, the embryo being nearly straight; and it has probably been distorted, as has also

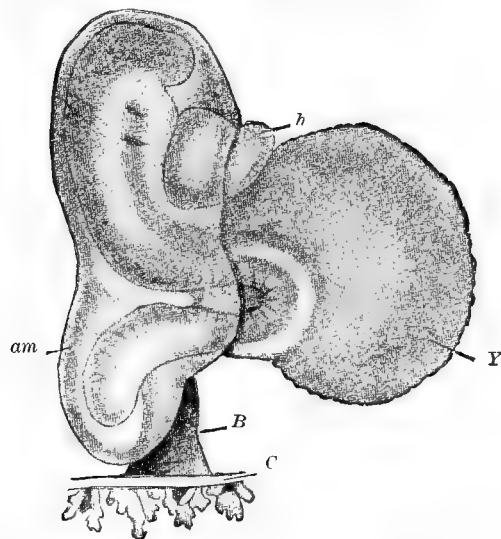


FIG. 5161.—Embryo Lg., 2.15 mm. Long. (Enlarged about 30 diameters.) am, Amnion; B, belly stalk; C, chorion; h, heart; Y, yolk sac. (His.)

4 mm. The brain increases in size and shows the three primary divisions. The optic and otic vesicles become more prominent. Two more gill clefts and three more gill arches appear caudal to the ones already formed. The attached area of the yolk sac has diminished. The

mouth cavity communicates with the pharynx. By the twenty-first day the limb buds appear (see Fig. 5162). Internally the heart is enlarged and takes the form of an S-shaped tube. From the aorta now arise five pairs of

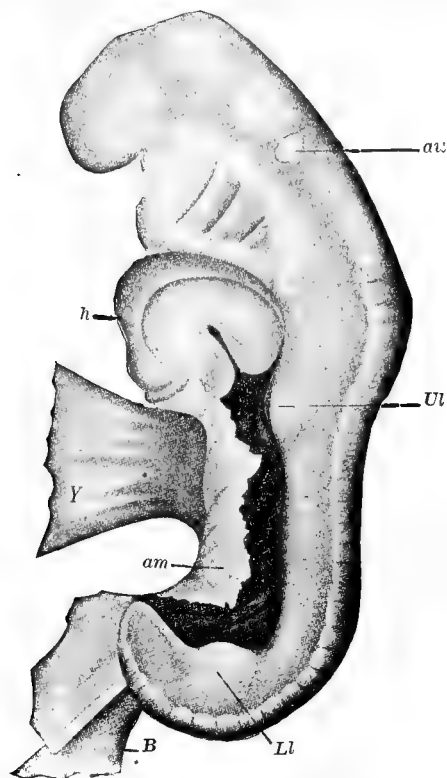


FIG. 5162.—Embryo Lr., 4.2 mm. Long. (Enlarged about 23 diameters.) *am*, Amnion; *au*, auditory capsule; *B*, belly stalk; *h*, heart; *Ll*, lower and *Ul*, upper limb; *Y*, yolk-sac. (His.)

arteries which pass through the five pairs of gill arches, joining on the dorsal side of the pharynx into the common dorsal aorta.

By the narrowing of the attachment of the yolk sac more of the primitive gut has been folded off, so that now the foregut, midgut, and hindgut are to be distinguished. In the foregut can already be made out the pharynx with its diverticula, the œsophagus, and the stomach. Of the pharyngeal diverticula there are four pairs of gill pockets corresponding to the gill clefts on the external surface and separated from the gill clefts by a thin membrane. The diverticulum for the respiratory tract has begun to bud from the œsophagus. The first indication of the lungs and trachea is found in embryos of about 3.2 mm. in length in the form of a groove, the pulmonary groove, along most of the ventral surface of the œsophagus. During the embryonal stage this groove deepens especially toward the stomach, where it ends in a rounded projection, which lengthens and gives off branches. These, by repeated branching, give rise to the various-sized bronchi and the epithelial portion of the lungs. The pulmonary groove gradually becomes constricted off from the œsophagus to form the trachea. At the upper end, however, it remains open into the pharynx, in the region of the fourth branchial diverticulum, to form the glottis. The midgut gives rise to the small intestine and to a portion of the large intestine. From it have arisen diverticula which give rise to the liver and pancreas. The hindgut gives rise to the rest of the large intestine and to the rectum.

The primitive urogenital system has appeared as two longitudinal ridges projecting into the coelom along its

dorsal wall, one at either side of the median line in the posterior half of the embryo. This ridge contains the Wolffian duct, the pronephros with its two tubules and rudimentary glomeruli. The Wolffian duct, which is the first to appear, develops from the mesenchyme, and extends from the heart region to the cloaca. Soon after the non-functional pronephros is formed, the mesonephros begins to develop and its tubules join the Wolffian duct. The mesonephros is a much more important structure than the pronephros, and we shall consider it again later. The beginning of the Müllerian duct is also present at this stage.

During the fourth week growth is relatively more active than at any other time, except during the very early stages of the first week or ten days. The embryo about doubles in length, and attains a length by the end of this week of about 6 or 7 mm. During the first part of the week the embryo becomes very much flexed, so much so that the head and tail nearly touch. The brain vesicles are better developed, as are also the gill clefts and arches, the eyes, ears, and nasal pits. The heart, which is much enlarged, lies in the cervical region, near the mouth, and produces with the liver, which is now of considerable size, a large ventral bulge. The simple tubular heart with its single cavity is rapidly changing into a complicated four-chambered structure with imperfect partitions. By the end of the fourth week (see Fig. 5163) the anterior enlarged portion of the head has become bent at right angles to the main axis of the body. From the first gill arch a maxillary process is developing which will ultimately form a portion of the upper jaw. From the main portion of the arch will form the lower jaw. The limb buds have increased in size. The arm bud projects from the cervical region and the leg bud from the lumbar region. The yolk sac is very small and the amniotic sac is much enlarged. During the early part of the fourth week the intestinal tube, composed of its several characteristic segments, lies in the sagittal plane attached to the dorsal wall of the body cavity by the straight primitive mesentery. Toward the last of the week rapid growth takes place, the intestine lengthens, and becomes coiled and twisted.

The nerves have begun to grow from the medullary tube or central nervous system into the mesenchyme. Plexuses are forming, but the nerves are not attached to their end-organs. There are now thirty-eight primitive segments or myotomes which have been formed from the mesenchyme lateral to the spinal axis. Muscle fibres are beginning to differentiate from the cells of these segments. Their ventral ends have begun to grow into the primitive abdominal wall formed by the growing around of the amnion. Condensed mesenchyme marks portions of the vertebral column. In the arm bud the mesenchyme is beginning to differentiate to form the skeletal core of condensed mesenchyme. The Wolffian ridge has increased in size and the Müllerian duct is now formed and runs parallel with the Wolffian duct. A diverticulum from the lower end of the Wolffian duct near the cloaca indicates the beginning of the permanent kidney and its duct, the ureter. On the Wolffian ridges are also seen the first traces of the sexual glands, but they are indifferent in type, and not until the fifth week can sex be determined by microscopical examination.

By the middle of the fifth week the embryo is 9 mm. in length. The amniotic sac is now so much enlarged that it is everywhere in contact with the chorion. A true umbilical cord of some length has developed by the enclosure of the entire belly stalk and yolk stalk within a tubular prolongation of the embryonic ectoderm and somatic mesoderm of the embryo. The embryonic ectoderm at the end of the cord is continuous with the extra-embryonic ectoderm of the amnion, and the somatic mesoderm with that of the amnion, which is in contact with that of the chorion. So, strictly speaking, the umbilical cord is a portion of the embryo, the amnion having been carried farther and farther from the umbilicus by extension of the embryonic ectoderm. The head is as large as the rest of the body, and bent at right angles to it. Its

large size is due to the rapid growth of the brain. The three primary divisions of the brain are more marked and bent upon each other. From the forebrain the cerebral hemispheres have begun to grow. The spinal cord forms a thick-walled tube of nervous tissue. The various cranial and spinal nerves now extend some distance into the body and the motor nerves of the head and shoulder reach the premuscle masses. The rami communicantes are already present at this stage and connect with the sympathetic cord. The latter forms a continuous column of cells in front of the vertebrae, and has not as yet separated into ganglia. The sympathetic nerve cells have reached this position by migration from the ganglia of the dorsal roots.

At about this time the suprarenals commence their development and are found, at the beginning of the third month, occupying their characteristic position as a cap fitted over the head of the kidney. They rapidly acquire a very large size and at birth have their permanent volume. There is no developmental relation between the suprarenals and the kidney. The suprarenals are probably derived partially from the mesonephros and partially from the sympathetic nervous system, the latter giving rise to the medullary portion and the former to the cortical portion.

The gill clefts and arches are undergoing marked changes. From the first arch the upper and lower jaws

portion of the cartilage of the first gill arch, and from its ventral portion Meckel's cartilage. From the second arch are forming the stapes, styloid process, and the hyoid apparatus, to which later the tongue muscles become attached. The remaining arches and clefts are beginning to disappear by sinking into the depth of the neck, re-

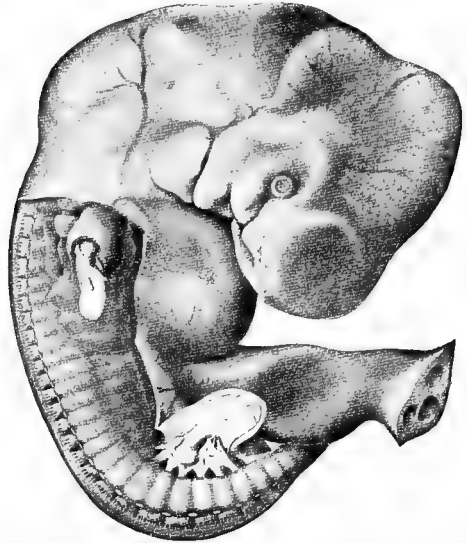


Fig. 5164.—Lateral View of a Human Embryo 9 mm. in Length and About Four and One-half Weeks Old. No. CLXIII. Johns Hopkins University Collection. (Enlarged about 8 diameters.) The areas from which the skin has been removed are drawn from reconstructions, the remaining portions from excellent photographs. The myotomes are growing into the body wall. Portions of the premuscle masses of the arm are seen and also the pre-skeletal tissue of the arm and leg with the beginnings of the lumbar sacral plexuses. (After Bardeen and Lewis.)

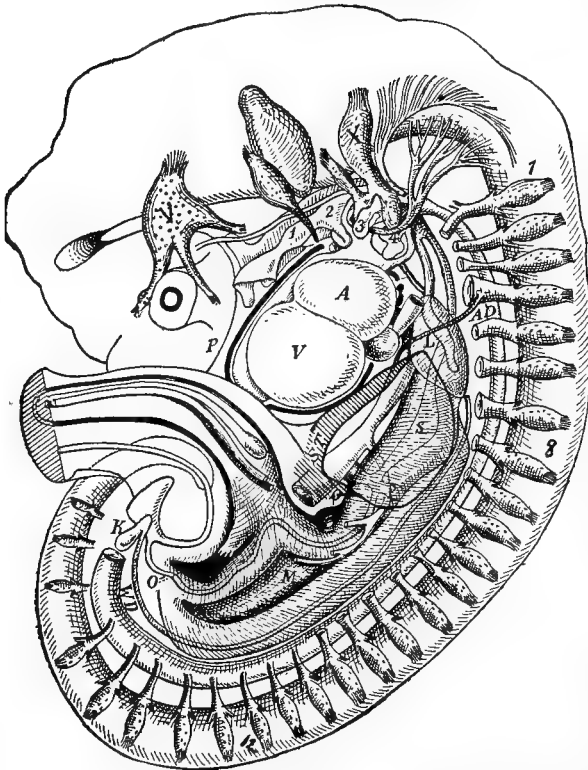


Fig. 5163.—Reconstruction of Embryo No. II., Johns Hopkins University Collection. (Enlarged 17 times.) V and X, Fifth and tenth cranial nerves; 1, 2, 3, and 4, cast of the branchial pockets; 1 and 8, first and eighth cervical nerves, from the fourth the phrenic arises; 12, twelfth dorsal nerve; A, auricle; V, ventricle; L, lung; S, stomach; P, pancreas; W D, Wolffian body; K, kidney; M, mesentery; S T, septum transversum; O, openings which communicate with the peritoneal cavity of the opposite side. The black line around the heart marks the pericardial cavity. (After Mall.)

are developing. From the first cleft the external auditory canal and ear drum are forming, and from the pharyngeal portion of the cleft the Eustachian tube and middle ear. The malleus and incus of the ear arise from the dorsal

maining connected with the surface, however, by a deep sinus, the so-called cervical sinus. Occasionally one may persist to adult life as a sinus or cyst. The arm and leg are enlarged and show two segments (see Fig. 5164). The skeletal system consists of a condensed mesenchymal tissue and precartilag. The premuscle masses of the head and arm are differentiating from the mesenchyme. Those of the trunk arising from the myotomes contain muscle fibres and are more advanced, while those of the limbs appear to develop *in situ* about the pre-skeletal mesenchyme, and show no fibrillation. The heart still lies close to the mouth in the neck region. It is much changed in shape and is imperfectly four-chambered. The truncus arteriosus is undergoing division into two tubes by the formation of the aortic septum.

The modification of the primary arterial system is progressing rapidly. The main portions of the first two arches have disappeared, giving rise with the third arch to the common carotids and their branches. From the last arch the pulmonary arteries are developing, and from the fourth, which seems to be a combination of the fourth and fifth, develop the large aortic arch on the left side and innominate and subclavian on the right side. The latter, however, still retains its connection with the dorsal aorta, giving a condition found in reptiles. The important connection of the last arch on the left side with the aorta remains of large size, and that portion of it between the pulmonary artery and the aorta forms the ductus arteriosus, a very important fetal structure, as it enables the venous blood from the right side of the heart to pass into the aorta without going through the lungs. The growth of the liver has also been an important factor in bringing about modifications in the venous system. With the diminution of the umbilical vesicle the extra embryonic portion of the omphalo-mesenterics disappears, but the embryonic portions of the two veins form the portal

system. Of the two umbilical veins, the left persists entire, to form the single umbilical vein of the embryo and cord. The right umbilical vein degenerates into an unimportant vein. The presence of the liver has also modified the proximal ends of the umbilical veins. The left one becomes divided into a capillary net, which

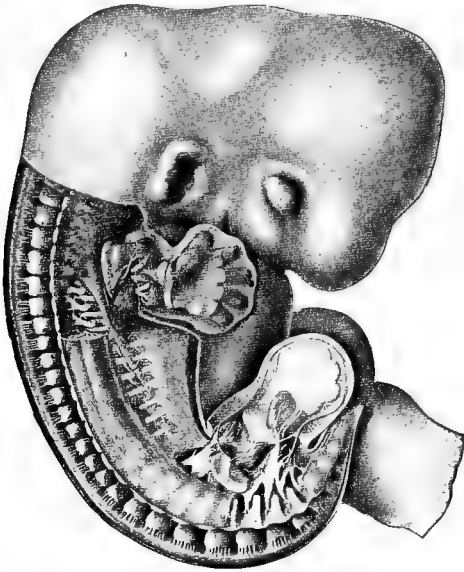


FIG. 5165.—Lateral View of a Human Embryo 11 mm. in Length and About Five Weeks Old. No. CIX., Johns Hopkins University Collection. (Enlarged about 7 diameters.) The dissected area was drawn from a reconstruction. (After Bardeen and Lewis.)

again collects into a short vein that opens into the sinus venosus. The development of the ductus venosus soon forms a channel for most of the blood carried by the umbilical vein. The proximal portion of the inferior vena cava is developed as a new structure. The distal end of this unites with the right inferior cardinal in the region where the renal arteries arise; and the caudal continuation of the cardinal from this point of union becomes the inferior portion of the vena cava. The remaining portions of the two cardinals form the azygos veins. A cross anastomosis develops from the left jugular to the right jugular, and from the common stem thus formed develops the superior vena cava. The proximal portion of the ductus Cuvieri on the left side then loses its connection with the jugular and becomes the coronary sinus of the heart.

By the time the embryo is five weeks old it has attained a length of 11 mm. (see Fig. 5165). The head is still very large and bent at right angles to the main axis of the body. The maxillary and nasal processes, which fuse at a later stage to form the upper jaw, are now more marked and approaching each other. The external nares are nearing the middle line. The external ear is represented by several small protuberances about the first cleft. The general body musculature is well advanced and has its nerve supply. The ribs and the muscles of the thorax and abdomen have grown some distance into the thin membrane, *membrana reuniens*, which in early stages constitutes the ventral body wall. The limbs are much enlarged and contain a skeletal core of cartilage surrounded by the developing muscles. The arm keeps about two weeks in advance of the leg in its internal differentiation. The vertebral column and ribs are formed partially in cartilage. The fourth pair of the aortic arches still persists entire and the others are modified in various ways to form the larger arteries in this region. The liver has been increasing rapidly in size, and in this embryo as in the preceding stage forms with the heart most of the large projecting abdomen and thorax. The

allantois forms a long narrow tube extending from the hindgut into the umbilical cord as far as the chorion. At a later stage the umbilical portion becomes obliterated, while the portion near the hindgut enlarges into the bladder.

During the fifth week the œsophagus elongates and the stomach acquires its characteristic form, as well as an obliquely transverse position, its former left side becoming directed anteriorly and upward, and its former right side looking backward and downward. This explains the distribution of the left vagus nerve to the front of the stomach and the right to the back; for, before this twisting of the stomach began, these nerves had already reached the stomach. The connection of the yolk stalk or vitelline duct with the intestinal canal rapidly becomes less marked, and by the end of this week only a small duct attaches the yolk sac to the intestine.

During the last part of the embryonal stage and the first part of the fetal stage there are very important shiftings or migrations of various organs in the body. That of the heart and diaphragm from the cervical region into the thoracic region is of especial interest, as other structures are dragged along with them. The large blood-vessels are pulled downward, and such nerves as the recurrent laryngeals indicate this process. Originally they passed directly from the vagus to the larynx just posterior to the fifth aortic arch, and by the migration of the heart and large blood-vessels they are brought into the position seen in the adult. The diaphragm in its descent obtains muscle tissue and its nerve in the cervical region,



FIG. 5166.—Drawing from a Reconstruction of a Human Embryo 20 mm. in Length and About Seven Weeks Old. No. XXII., Johns Hopkins University Collection. (Enlarged about 5 diameters.) The muscular systems of the limbs and body wall are seen to be well developed. (After Bardeen and Lewis.)

and both are then carried down to the lower part of the thorax. The limbs also exhibit a migration, the arm from the cervical to the thoracic region giving the caudal inclination to the brachial plexus, which originally went straight out into the arm without this caudal inclination. The leg likewise migrates. Many individual muscles also take part in this shifting and migrating, such as the trapezius from the upper cervical region and the

latissimus dorsi from the lower cervical. The path of the nerve from its exit at the intervertebral foramen to its point of entrance into the muscle indicates the path the migrating muscle has taken, while the branching within the muscle probably indicates the direction in which the muscle has increased in size.

During the embryonal stage the yolk sac has diminished to an organ of relatively small size and importance, while the central nervous system, with its greatly enlarged anterior end, the brain, giving to the head its great prominence, becomes the predominating feature of the embryo. The head throughout most of this stage is about equal in bulk to the rest of the body of the embryo.

Fœtal Stage.—In an embryo seven weeks old and 20 mm. long the early fœtal features are fairly well marked. The head is nearly erect. The fusion of the maxillary and nasal processes is proceeding rapidly to form the upper jaw, and the nasal pits have approached nearer to the median line. Failure of fusion between these processes gives rise to the various forms of cleft palate and harelip. The arms and legs are much elongated, and show the three segments seen in adults. Fingers and toes are also to be distinguished. Practically every muscle of the body can now be recognized, and has also its nerve supply (see Fig. 5166). Most of the skeletal elements are present in cartilage. Portions of the skull, however, are never so represented, but ossification takes place directly from the condensed mesenchyme. The ribs have extended nearly to the mid-ventral line. The thoracic and abdominal muscles have likewise pushed farther out into the ventral wall of the body.

By the end of the second month the permanent kidney is fairly well formed and the Wolffian body, which so far in the life of the embryo has performed the function of an excretory organ, begins to lose its importance. All but the middle portion, which later forms the sexual gland, atrophies. Its duct in the male forms the vas deferens, in the female degenerates, while in the female the Müllerian ducts form the Fallopian tubes and uterus, and in the male degenerate. Thus by the end of the second month most of the organs which are found in the adult are formed. The main processes which now take place until birth are the growth and shifting about of these organs.

The *third month* establishes the human form, although the head still unduly predominates. The limbs have acquired their definite shape, and the imperfect nails are present on both fingers and toes. The external organs of generation become definitely differentiated, although they make their appearance several weeks earlier.

In the female the genital tubercle remains much less developed to form the clitoris. The genital furrow remains open to form the vestibule and the genital swellings the labia majora. The prepuce and labia minora developing from the genital folds, lie at either side of the genital sinus. The genital swellings in the male when they develop into the scrotum have layers identical with those of the abdominal wall, as seen in the following scheme:

<i>Abdominal Walls.</i>	<i>Scrotum.</i>
Integument.	Integument.
Superficial fascia.	Dartos.
External oblique muscle.	Intercolumnar fascia.
Internal oblique muscle.	Cremasteric.
Transversalis muscle.	Infundibuliform fascia.
Peritoneum.	Tunica vaginalis.

The tunica vaginalis lines the sac, communicating above with the peritoneal cavity; and into this sac later the testicle descends. The anterior end of the ureter now reaches the neighborhood of the suprarenal where it ends in the kidney, which consists of about eighteen lobes, one for each group of tubules connected with the ureter. This lobulation persists until after birth. The suprarenals now fit caplike over the anterior end of the kidney. At the end of the month the fœtus weighs about 120

gm. ($3\frac{1}{2}$ ounces), and measures about 5 cm. (2 inches) in length.

During the *fourth month* hairs devoid of pigment appear on the scalp and other parts of the body, which is now covered with firmer skin of a rosy hue. The eyelids, nostrils, and lips are closed. The anus opens, and the coils of intestine, which before extended into the umbilical cord, now lie entirely within the abdominal cavity. The point of emergence of the umbilical cord lies low down close to the pubes. The head forms about one-fourth of the entire body. The bones of the skull while ossifying are still widely separated. The sexual distinctions of the external genital organs are well defined. By the end of this month the fœtus weighs about 230 gm. ($7\frac{1}{2}$ ounces), and measures about 10 cm. ($4\frac{1}{2}$ inches) in length.

During the *fifth month* the lower extremities become longer than the arms, nails are well formed, and hairs are more plentiful, but devoid of color. The fœtal movements are distinctly felt by the mother. The sudoriparous glands arise during this month as solid cylindrical outgrowths from the primary ridges of the epidermis into the dermis. Later they become coiled and a lumen appears. The heart and liver share with the head in the undue preponderance which these parts present. At the end of this month the fœtus measures 20 cm. (8 inches) in length, and weighs about 500 gm. (1 pound).

During the *sixth month* the surface presents many wrinkles and is of a dirty reddish hue; the sebaceous coating, the vernix caseosa, begins to appear. This whitish substance is composed of shed surface epithelium, mingled with the secretions of the sebaceous glands; its primary function seems to be the protection of the integument from maceration by the amniotic fluid. The eyebrows and eyelashes begin to grow. The length of the fœtus by the end of this month is about 30 cm. (12 inches), and its weight about 1,000 gm. (2 pounds).

The *Seventh Month.*—The formation of fat causes an appearance of greater plumpness, although the surface is still somewhat wrinkled. The hairs are longer, about 5 mm. in length. The eyelids are now permanently open. The liver is still relatively large; the testicles have descended as far as, or even into, the inguinal canals. Children born at the end of this month may live. The fœtus measures at the end of this period about 37 cm. long (15 inches), and weighs about 1,500 gm. (3 pounds).

The *Eighth Month.*—This and the ninth month complete the fœtal period. The chief changes are great increase in weight, as by the end of the eighth month the fœtus weighs from 2 to 2.5 kgm. (4 to 5 pounds) and measures about 42 cm. in length. The scalp is well supplied with hair, and the finger nails almost reach the finger tips. The lanugo or embryonal down begins to disappear. The subcutaneous fat has increased considerably, giving a more rounded form to the body.

The *Ninth Month.*—During this month there is a relatively large increase in weight, from 2 to 2.5 kgm. to about 3 or 3.5 kgm. (6 to 7 pounds), while the increase in length is only from about 42 to 50 cm. (20 inches). The skin is less highly colored and the lanugo has almost entirely disappeared. The testicles have descended into the scrotum; in the female the labia majora are in contact. Centres of ossification usually appear in the epiphysis at the lower end of the femur, and often in the upper epiphyses of the tibia and humerus.

Warren Harmon Lewis.

FOURTH DISEASE.—It is to Clement Dukes that we owe this addition to the number of contagious exanthemata. Led by his experience extending over a number of years at Rugby School, Dukes published in *The Lancet* of July 14th, 1900, his original paper on this subject with the title "The Fourth Disease; or, the Confusion of Two Diseases under the Name of 'Rubella.'" In this paper Dukes states that he had for several years suspected the existence of another contagious exanthem, but that he was not convinced of it until the advent of an epidemic in April, 1900. His reasoning is as follows.

German measles appears under two forms—one resembling measles, and the other resembling scarlet fever; an attack of one form of the disease does not protect the patient from an attack of the other form. He has never observed the slightest tendency of the fourth disease to develop into true scarlet fever, although this disease does closely resemble mild scarlatina. It is important to distinguish the fourth disease from scarlet fever chiefly because of the difference in the time of quarantine, especially in schools.

Epidemics of so-called German measles at one time resemble scarlet fever; at another time all of the cases resemble measles.

The measles form of German measles usually affects large numbers of those exposed, while the fourth disease, like scarlet fever, affects a limited number, being apparently, like scarlet fever, least infectious at its onset. Moreover, cases of fourth disease occur in children who have previously suffered from scarlet fever.

Certain studies made by Dukes may be cited to bear out his contention of a fourth disease. In the year 1892 he was called to see sixteen cases of illness supposed to be scarlet fever, and he decided that it was the scarlet-fever variety of rubella, or what he later called Fourth Disease. The lads were in school and were sent to their homes. Subsequently, there was not a single instance of scarlet fever reported among the boys who went to their homes for the holidays; but one of the nurses after going home suffered from what was diagnosed as a genuine case of rubella.

The second study was that of a concurrent epidemic of scarlet fever and fourth disease. In this instance the fourth disease preceded the onset of the scarlet fever by twenty days. Some of the boys had scarlet fever only, others had fourth disease only. One had scarlet fever first, and afterward fourth disease; and still others had fourth disease, followed by scarlet fever. Among those cases diagnosed as scarlet fever two of the boys died.

Another study was made at Rugby in March and April, 1900—nineteen boys being affected by fourth disease, nearly one-half of whom previously suffered from rubella. Twenty days after the onset of the epidemic the school was dispersed. Of all these boys who went to their homes, there was only one who had a malady diagnosed as scarlet fever.

The symptoms may be grouped as follows:

Incubation Period.—Varies from nine to twenty-one days, resembling rubella and differing markedly from scarlet fever.

Prodromal Symptoms.—Usually about, though occasionally chill, nausea, headache, backache, and loss of appetite are present.

Eruption.—The first symptom to attract attention is the rash, which in nearly every case is full and quite characteristic of scarlet fever, being small and thickly set, pale red, and scarcely raised above the surface. It may cover half of the body in a few hours.

Throat.—The fauces are red and swollen, but there is little or no complaint. No matter how severe the eruption—and “in many cases it resembled the worst eruption in scarlet fever,” says Dukes, the throat never looks like that seen in a well-marked case of scarlet fever. The lymph nodes of the neck are swollen, hard, and about the size of a pea. In some cases the axillary and inguinal nodes are enlarged.

Desquamation.—Usually there is free desquamation of small scales; but in a few the peeling was equal to that in scarlet fever. In this “fourth disease” the desquamation bears no relation to the intensity of the eruption. Nephritis is a rare sequel; but a trifling albuminuria may be present.

General Symptoms.—The pulse rate is unaffected; the temperature ranges from 98.4° to 104° F.

Infectiousness.—At the onset it is only slightly contagious, and the infectiousness disappears entirely in two or three weeks.

Since the publication of Dukes' paper there has been

world-wide discussion of the subject with a great deal of scepticism. It is to be said, however, that in 1885 Nil Filatow raised the same questions as Dukes, and that in 1896 he outlined a separate disease similar to the “Fourth disease.” Moreover, J. J. Weaver furnishes support to Dukes' contention. Some months prior to Dukes' publication he noted in the Southport Infectious Disease Hospital, within three months after a number of scarlet-fever cases, recurrences with a new eruption and fever. He reported fourteen hospital cases with their temperature charts. These are of special interest because they are cases in which fourth disease either preceded or followed scarlet fever. Many writers dismiss the subject by saying that the cases are merely mild cases of scarlet fever. The general verdict seems to be that there are needed many confirmatory observations of epidemics before the disease can be accepted as established.

Linnæus E. La Fêtra.

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GANGOSA.—The feminine form of a Spanish adjective meaning “nasal-voiced.” This word has been erroneously used as a name for the disease *Rhinopharyngitis mutilans*, q.v.

J. F. L.

GIGANTISM, GENERAL.—The word giant is derived from the Middle English “geant,” the equivalent of the French “géant,” which may be traced back to the Greek γίγας.

Very early in the world's history we meet with references to huge beings of supernatural strength. Even before the flood, in the story of Noah, we are informed that “there were giants in the land in those days,” and there are stray allusions to giants, Emmim and Anakim, in the accounts of the early Jewish conquests, in the sight of whom the people were “as grasshoppers,” to use the characteristic Eastern hyperbole. Later, we have the celebrated battle between David and Goliath of Gath, one of the few remaining descendants of these Anakim, whose height was six cubits and a span. The Greeks, also, had their giants in the man-eating Cyclopes and Lestrygonæ. The Titans, too, forty-five in number, whose children were the Gigantes, were of enormous size. They did not fear to encounter the gods, and were said to have heaped up mountains, to have “piled Ossa on Pelion,” in order to scale the heavens. All nations, alike in their love of the marvellous and their sympathy with the weaker side, have their stories of unequal battles, recalling the struggle between the pygmies and the giants, waged between brave men and monsters of immense size and strength, in which the lesser power comes off the conqueror. An instance that will be familiar to all is the popular nursery tale of “Jack the Giant-killer,” which used to delight us so much in our youth. As is usually the case, human credulity and the innate tendency to exaggeration have magnified many of these tales beyond the bounds of credibility. While it must be admitted that in former times there have been individuals and even races that far exceeded in strength and stature the ordinary run of mankind, the application of the rigid canons of modern scientific inquiry has resulted in the dethronement of the supernatural element and the reduction of the subject, though marvellous enough still, to more manageable proportions. Before passing on to discuss the nature of this curious anomaly of development that we call gigantism, we may with advantage pause for a moment to determine what constitutes giant growth.

This is not so easy as it seems. If any one asks himself the question, “Where does giant growth begin?” he will at once realize that his ideas are somewhat hazy and his language conventional. In popular parlance a giant may be said to be any individual who exceeds in a notable degree the average height of human beings. A per-

son of six feet six or upward would probably be called gigantic. This is, of course, an exceedingly loose and by no means scientific definition. It fixes no limits, it takes no account of weight and strength; in short, it lacks precision. Larcher¹ defines a giant to be "A being who, free in other respects from all defect in the essential characteristics of the organization, excels notably in height other beings of the same race who have reached adult age." In such a case the structural harmony and the relationships between the different parts are manifestly normal, the sole deviation being the striking increase in height. It is scarcely necessary to point out that this definition portrays for us the ideal or perfect giant, a being rather more imaginary than real. No doubt there have been individuals of great size and strength, handsome, well proportioned, and well balanced in all their faculties, but these are the *rare* or rather the *rarissimæ* *aves*. As a matter of fact, the immense majority of giants present the unmistakable stigmata of defect or degeneration. The definition further ignores the fact that gigantism is a process, an anomalous one it is true, but still a process of growth which may and does manifest itself in embryonic life and childhood, as well as in the adult stage. Pierre Marie² recognizes two forms of gigantism: (1) *True gigantism*, consisting in a simple exaggeration of the normal process of growth; and (2) *symptomatic gigantism*, a manifestation of pre-existing disease. Meige³ would restrict the term gigantism to Marie's second class on the ground that the members of the first group are in all respects normal persons, differing in no way, save in height, from other individuals of the same species. This, while no doubt contributing to precision of language and lessening the possibility of confusion in description, is in my opinion too extreme a position to take, for who will maintain that an exaggeration of a normal process of growth is not a pathological manifestation? We ought not, therefore, rashly to conclude that true gigantism and symptomatic gigantism are necessarily or essentially different processes, or that the former should be left out of our consideration of the general subject of gigantism. We shall be helped considerably toward a proper conception of what constitutes giant growth if we consider briefly what may be called the "law of deviation" enunciated by Thoma.

Thoma⁴ states, on the basis of an extended series of observations, that in adults the normal length of the body averages approximately 169 cm. in the male and 163 cm. in the female; the normal average body weight is 60 kgm. and 56 kgm. respectively. Considerable variations on one or other side of this norm occur. In one-half the total number of individuals the amount of deviation is anywhere from 0.0 to 3.8 cm. for height, and from 0.0 to 5 kgm. for weight. In accordance with observations he has made, Thoma finds that the fifth multiple of the figures representing the amount of normal deviation, namely, 19 cm. and 25 kgm., is exceeded only once in a thousand individuals. According to this an adult male would be regarded as a giant if his height exceeded 169 plus 19 or 188 cm., or if his weight were more than 60 plus 25 or 85 kgm. The normal limits, however, for the upper well-nourished classes are somewhat higher than the figures given, namely, 175 cm. and 66 kgm., so that the lower limit for giant growth would be more correctly placed at 175 plus 19 or 194 cm., and 66 plus 25, or 91 kgm. (6 feet 4½ inches, and 200 pounds 5½ ounces). In the case of new-born infants the normal average for length is 50 cm. and for weight 3.2 kgm. The amount of deviation is approximately 1.4 cm. and 0.28 kgm. respectively. Applying the same rule we may assume giant growth in children if they exceed 57 cm. in length and 4.6 kgm. in weight. For Thoma, then, a giant is literally a man in a thousand. We cannot, however, assume that because an individual exceeds these dimensions he is necessarily a giant. It should be noted that height and weight are not necessarily closely correlated. In true gigantism no doubt they would be, but in many cases we find that those gigantic in stature are not heavier than many normal

persons. This is often to be explained on the score of some wasting disease which is present, or that the individuals in question have died or been observed before the consolidation of the body had been properly attained. Further, an excess in weight above the limit of 91 kgm. cannot in itself constitute gigantism, for this weight is frequently attained by those who would be regarded as normal individuals, and has also been attained in cases of diffuse lipomatosis, elephantiasis, and when large tumors are present. Gigantism is quite different from this. Properly understood, it implies not a mere increase in the bulk of any tissue or group of tissues, but rather an abnormal increase in the size of the body as a whole, due to some peculiar and inherent nutritive disturbance. The term *macrogenesy* would perhaps most correctly designate the condition.

Gigantism manifests itself in an excessive growth of the bones, more especially in the direction of length, but also to some extent in thickness. The long bones are most noticeably involved, but all the bones of the body may be to some degree affected. With this there is a corresponding increase in size of the nerves, vessels, and soft tissues generally. The most striking and constant feature in giants, however, is their great height. The deviation in weight is less apparent, is usually less and never more than the increase in height would warrant.

From a pathological standpoint gigantism belongs to the group of tissue hypertrophies, of which there are many less extreme manifestations than the complete giant. Local hypertrophies of undoubtedly developmental origin are not infrequently met with, particularly in the head and extremities. In the case of the head the bones of the cranium and face are usually involved, giving rise to an extensive and remarkable deformity (leontiasis ossea of Virchow), the exact nature of which is somewhat obscure but appears to be essentially a diffuse hyperostosis. The form found in childhood is especially common in the upper limbs, and may be unilateral or bilateral. Apart from these instances of local gigantism, which are characterized mainly by an abnormal increase in the bulk of the affected part, there are other conditions, regarded by some as forms of gigantism, in which the excess is numerical, as, for example, polydactylism, accessory ribs and vertebrae, and supernumerary organs.

Gigantism, or macrogenesy, is comparatively rare as a congenital anomaly. Fuchs⁵ in the extensive material of the Lying-in Hospital at Kiel found the average weight of the new-born child at full term to be from 3 to 3.5 kgm., figures which agree accurately with those given by Thoma. This limit was not often passed, and a body weight of 5 kgm. (11 pounds) was of the greatest rarity. In 3,600 births at the Dublin Rotunda only one child reached 5 kgm. Ahlfeld⁶ in fifteen years' experience met with no case above 5.1 kgm. Spiegelberg and Wiener⁷ observed two infants weighing 5.2 and 6 kgm. respectively. Baudelocque⁸ in many years saw only one infant that reached 6.375 kgm. Fuchs (*loc. cit.*) has described in detail two infants that weighed 6.1 and 7.55 kgm. and measured 60 and 65 cm. respectively. The most extensive statistics are those of von Winckel,⁹ who in 30,000 births found no child reaching 6 kgm.; in 17,000 cases at Munich only 5 were found weighing from 5 to 5.32 kgm. These dimensions, striking as they are, have been considerably surpassed by some found in English and American literature. Eddowes¹⁰ mentions the birth of a child weighing twenty-two pounds two ounces. The mother was thirty-three years of age, and had previously borne two children of large size. Chubb¹¹ met with one case in which the child weighed twenty-one pounds. The other children of the family were exceptionally large. The fact that some women have a tendency to bear large children is also well illustrated by an observation of Dickinson's,¹² where a woman was delivered by craniotomy and evisceration of a child weighing sixteen pounds. Her first child weighed nine pounds and her second twenty. Beach¹³ records the birth of the child of Captain Bates and Anna Swann, both of gigantic proportions, which weighed twenty-three pounds twelve ounces.

Baldwin²⁵ quotes the case of a woman who after having three miscarriages finally had a child weighing twenty-three pounds. There are at least ten other instances on record of new-born children weighing from thirteen to twenty pounds. The largest child I have been able to find recorded is a case of Dubois,¹⁵ which attained the almost incredible weight of 11.3 kgm. (24 pounds 13½ ounces).

As will readily be understood, the fate of giant children is often an untoward one. Not infrequently they die in the later months of gestation. When brought to term, they have to be delivered by operative interference of some kind, and are often still-born. It is an interesting fact that the dystocia is brought about, not by the head, which usually, unless hydrocephalic, does not exceed in size that of a normal child, but by the size of the trunk. The biacromial diameter is excessive. In Dubois' series of forty-four cases only twenty-six were born alive. Children of 8 kgm. and over are invariably still-born. In those that survive, the excessive size at birth is sometimes compensated for by slow growth subsequently, but the pathological nature of the process is sufficiently indicated by the fact that such children often grow very fast and attain puberty in the third to the sixth year. It is perhaps questionable whether all cases of precocious development, wherein the individual attains the structural and functional characteristics of the adult in early childhood, are to be regarded as manifestations of gigantism. Some at least have this in common with gigantism that they show evidences of early senility. Development is rapid and decay is premature. Phlegmon ("De Mirabilibus," cap. 32) is the authority for the statement that Craterus, the brother of King Antigonus, was an infant, a young man, married and begat children, and became an old man in the short space of seven years. In 1741 a boy was born at Willingham, near Cambridge, who when twelve months old presented all the appearances of puberty and died an old man at the age of five years (Philos. Trans. of the Royal Soc. of London). The subsequent history of unusually large children is unfortunately not often to be traced, but there is some slight evidence to show that they may develop into gigantic adults. Bonardi¹⁶ reports an interesting case which throws some light upon this point. A boy at the age of fifteen had the size and development of an adult male. At twenty-two he began to suffer from pains in the head with nausea, and soon after the hands, feet, maxillæ, and tongue began to increase in size. At the age of twenty-nine he measured 194 cm., and presented all the signs of acromegaly. In other instances, too, the abnormal increase in size has been known to begin quite early. Gilbert of the Hôpital Broussais (quoted by Meigs, *loc. cit.*, p. 449) met with an individual who began to grow rapidly after an attack of some acute fever in his earliest infancy and eventually attained the height of 196 cm. The American giant Wilkins began to grow rapidly at the age of four, and reached his full height (245 cm.) at eighteen. As a rule, however, the excessive growth does not become in evidence until some time between the tenth and twentieth years, usually with the onset of puberty.

The student of ancient lore will be interested and amused to see how superstition and the love of the marvellous have combined to render many of the accounts of giants that have come down to us thoroughly unreliable. Judging from these stories, the height to which the human race may attain has varied between wide limits. Pliny, like Augustine, believed that the stature of mankind had deteriorated, but this is not substantiated by the examination of such ancient remains as we possess. The rabbinical legends teem with incredible accounts of the height of the various Biblical characters. Adam's height was calculated to be one hundred and twenty-three feet and Eve's one hundred and eighteen. According to the Biblical account the bedstead of Og, King of Bashan, was nine cubits long. Pliny mentions the giant Gabbaras, between nine and ten feet high, who was brought from Arabia by the Emperor Claudius, and states further that the remains of Posio and Secundilla,

found in the Sallustian Gardens in the time of Augustus Cæsar, measured each ten feet three. Josephus refers to a Jew nearly eleven feet high, who was sent as a hostage to Rome by the King of Persia. Some remarkable stories are told of the Emperor Maximin (C. Julius Verus Maximinus) who was born in 173 in one of the frontier villages of Thrace. A shepherd in his youth, he soon became noted for his extraordinary height and strength. He took part in the games given by Septimius Severus to celebrate the occasion of the birth of his son, and overcame sixteen of the most powerful wrestlers without taking breath. The Emperor attached him to his own person and he was made a centurion by Caracalla. Capitolinus says that he was a finger's breadth over eight feet in height. His thumb was so large that he could use his wife's bracelet for a ring. He stopped a wagon with one hand, broke the jaw of a horse with a blow of his fist, and could break its leg with a kick. He is credited with eating forty pounds of meat in a day and used to drink as much as a Capitoline amphora (about twenty-six litres). He became tribune under Alexander Severus, and, conspiring against him later, was elected emperor. He reigned for three years, execrated for his cruelty, and was finally assassinated by the soldiers in 238.

Coming to more recent times, we have some equally extraordinary tales brought back by travellers. Magellan is said by some to have given the name Patagonia to the country he discovered because its inhabitants measured five cubits. Lemaire, in describing his voyage in 1615 to the Straits of Magellan, states that at Port Desire he found several graves covered with stones in which were skeletons of men measuring from ten to eleven feet. More recent travellers have, however, found the Patagonians to be not excessively large; in fact many of them are rather diminutive. The naturalist Turner believed that he saw on the River Plata near the coast of Brazil savages twelve feet high. Accounts more marvellous still are given of giants from nineteen to thirty-six feet high, who have existed at various times in Europe. These are based on the discovery of bones of prodigious size, which were erroneously regarded as human. In those days nothing was known about comparative anatomy, and the remains in question were no doubt those of some of the lower animals. Sir Hans Sloane, in an elaborate and learned disquisition on the subject, came to the conclusion that the bones referred to were parts of whales, mastodons, elephants, or other enormous beasts, although he thought that some of the stories could not be entirely discredited. It is a fact, however, that in more recent times, when such matters are much more narrowly scrutinized, no such instances of excessive height can be substantiated. Buffon, the great naturalist, usually a reliable authority, had no doubt that human beings had existed who were from ten to fifteen feet high. It is not until we come to the eighteenth century that we get reliable data as to the height of giants. According to Dana¹⁶ not more than a hundred giants have been exhibited in public since 1700, and of this number only about twenty were said to have been over eight feet. Topinard measured the tallest man in the Austrian army, and found him to be eight feet four and a half inches. Winckelmeyer was eight feet six inches. Marianne Wehde, a more recent German giantess, was eight feet four and a half inches when sixteen and a half years old. In view of these observations we must seriously question whether any human being has ever exceeded nine feet in height. Quite a number of giants have been recorded who measured between seven and eight feet, but above this limit the cases are extremely few. The history of these is often extremely interesting. Queen Elizabeth's porter, whose portrait, painted by Zuccherro, is now in Hampton Court Palace, was seven feet six inches high. Walter Parson, the porter of James I., was as big. William Evans, the porter of Charles I., was about eight feet high. Cromwell's porter, Daniel, who died a lunatic, attained the height of seven feet six. In the reign of George I., an Englishman, seventeen years old and eight feet tall, was exhibited at the Bartholomew Fair at

Smithfield. "Big Sam," the porter at Carleton Place when George IV. was Prince of Wales, was eight feet in height. In a Dutch village in 1712 there died a fisherman called Gerrit Bastiaansen, who measured eight feet and weighed five hundred pounds. As a contrast to this we may cite a giant who was exhibited at St. Petersburg in 1829, who measured eight feet eight, but withal was thin and emaciated.

One of the most celebrated giants was Cornelius McGrath, whose skeleton is now in the museum of Trinity College, Dublin. He was born in 1736 in the county of Tipperary. His parents and the other members of the family were of ordinary size. After the age of fifteen he began to suffer from violent pains in the limbs and began to grow rapidly. At the age of sixteen he was six feet nine. In 1753, six months later, when he first exhibited in public he measured seven feet three inches in his stocking feet. It is said that he was ungraceful in appearance, of low intelligence, and spoke in a childish manner. He died at the early age of twenty-four. His skeleton measures seven feet eight inches.

John Middleton, called the "Child of Hale," was born in 1752 at Hale in Lancashire. His portrait is preserved in Brazenose College. He is said to have measured nine feet three inches.

O'Brien or Byrne, the "Irish Giant," is celebrated not only for his great height, but for his connection with the distinguished anatomist John Hunter. Hunter was particularly anxious to secure his body and made the most extraordinary exertions to obtain it. O'Brien was aware of this desire on the part of the anatomist and was correspondingly averse to being "set up" as a specimen. Shortly before his death, which occurred at the age of twenty-two, O'Brien bribed some of his friends to take his body, and after weighing it with lead to sink it in the sea. The undertaker, however, who had been previously interviewed by Hunter, managed to have the coffin locked up in a barn while the escort was refreshing at an inn. Thereupon some men, stationed there for the purpose, substituted an equal weight of paving stones for the body which was forwarded that night to Hunter. He took it in his carriage to Earl's Court, where it was immediately prepared. It is estimated that it cost nearly five hundred pounds to secure the body. O'Brien is said at the time of his death to have been eight feet four inches high. His skeleton, however, measures only seven feet seven. It is now, together with the kettle in which the body was boiled, in the museum of the Royal College of Surgeons in London.

The successor of O'Brien, Patrick Cotter, who for a time exhibited under his name, was born in 1761. At his death, which occurred at the age of forty-five, he is variously estimated to have been from eight feet one to eight feet seven in height. At one time he was examined by Dr. William Blair, who found him to measure about seven feet ten. He was badly proportioned, and looked like a weakly or even imbecile person. His forehead was low, his pulse feeble, his voice weak, and he suggested in appearance a sickly child that had grown too fast.

Robert Hale, the "Norfolk Giant," who died at Yarmouth in 1843 at the age of forty-three, was seven feet and a half high and weighed four hundred and fifty-two pounds.

Among the better known of the exhibited giants were Captain Bates, of Kentucky, and his wife, Anna Swann, of Nova Scotia. Captain Bates enlisted in the Southern army at the beginning of the American Civil War, being readily accepted on account of his size, although he was only sixteen years of age. By the end of the war he had attained the height of seven feet two and a half inches. He gradually increased in weight also until he turned the scale at four hundred and fifty pounds. While in England in 1871 he married at St. Martin's-in-the-Fields Miss Anna Swann, who measured seven feet five and a half inches. On neither side were the parents of more than ordinary stature.

Chang, a celebrated Chinese giant, died at Bourne-

mouth in 1896, at the supposed age of fifty-one. He was upward of eight feet high.

At the Alhambra in London in 1882 was exhibited the "Queen of the Amazons," who was eighteen years old, and measured eight feet and half an inch.

We owe much of our present knowledge of the processes of growth and development to the epoch-making work of Winslow, Haller, Meckel, and the Saint-Hilaire, father and son. Although of late the interest of scientific men has been somewhat revived in the subject we cannot as yet be said to have made much advance, except that we are beginning to apprehend more fully the nature of the problems involved. We are now realizing the fact that growth and development are a very complicated matter. We see, for instance, that we must draw a distinction between mere growth, or what may be called vegetative force, function, and reproductive power. These three factors are more or less correlated, but the correlation often varies both in kind and in degree. Certain cells are specialized for growth, others for function, others for proliferation. All cells may at some time in their life history be specialized in one or other of these directions according to the demands made upon them, but they cannot be specialized in all three directions to the same extent at the same time. Thus a cell that is about to divide ceases to grow and enters into a resting stage before mitosis occurs. And other illustrations might be given. Moreover, what is true of the cell is true of the community of cells known as the individual. Up to a certain period of life the forces of the body are concentrated toward the main object of growth. Later, function becomes more in evidence. Last of all the power of reproduction becomes established and perfected. In gigantism disturbance of growth in the direction of increased stature and weight is the predominant feature, but, as we shall see, this does not occur as a rule without exacting a corresponding penalty in the degradation of the general bodily functions and the power of reproduction. The causes which lead to this result may be inherent in the germ cells so that they make their influence felt quickly in the construction of the organism, or they may become operative subsequently to fertilization and segmentation of the ovum, either during intra-uterine life or after birth. These influences may, further, be exerted upon the body as a whole or on some part of it. There is therefore a family relationship between gigantism, dwarfism, and the various malformations and monstrosities. In both dwarfism and gigantism, which are not, as might at first sight be supposed, perfect opposites one of the other, there is not merely an inhibition or an exaggeration of the normal processes of growth, but in the vast majority of cases something more, namely, a perversion of growth. In the normal infant at birth, the head and trunk, but particularly the head, are relatively large. As the time of puberty approaches the picture changes. Growth is rapid and irregular. The limbs are now disproportionately large, the hands and feet being especially prominent. To use a common expression the child has become the hobbledoy. Only in the later period of puberty does the trunk enlarge, the figure consolidate, until the perfect proportions of the adult are attained. There is a striking parallel between the hobbledoy stage and what we find in gigantism. In giants the exaggeration of growth is also disproportionate and irregular. The head is often small, or at least about the same size as the head of a normal youth or adult of the same age; the increase in height is mainly due to the excessive growth of the lower extremities as compared with the rest of the body. Here, however, the parallel ceases. Giants are often weakly rather than strong; the sexual organs are apt to be badly developed, and the sexual proclivities are sluggish or delayed. They are liable to contract disease and show signs of premature senility; in fact they rarely reach middle life. Dwarfs, on the contrary, are long-lived. They frequently have the relatively large head of the infant, with evidences of delayed ossification of the cartilages, and genital inadequacy, facts which have caused many to

regard dwarf growth as really infantilism. Unlike the giants they frequently possess average or more than average mental powers. It is clear that in both gigantism and dwarfism the disturbance, whatever it is, manifests itself mainly in the rate and extent of the growth, but still to a noteworthy degree in disordered function. And it is not merely the process of ossification that is at fault but the body as a whole—bones, soft parts, and internal organs—is involved. Nevertheless the disturbance of ossification appears to be the controlling force, for it undoubtedly dominates the picture.

Normally, the growth of bone depends on the activity of certain specialized cells—the osteoblasts—which are chiefly situated in the deeper layers of the periosteum, at the extremities of the bones, and along the interosseous sutures. Growth in thickness takes place from subperiosteal osteoplasia; growth in length is due to the influence of the osteoblasts in the spongy ends of the bones and in the epiphyseal cartilages. Inhibition or exaggeration of stature is due in the main to dystrophic changes at the extremities of the long bones, although subperiosteal osteogenesis is also to some extent interfered with. The results depend not only on the inherent vegetative forces at work in the cells, but on the condition of the epiphyseal discs. So long as the discs are movable, growth in length of the bone is possible. This is interestingly borne out by recent investigations with the x-rays in certain forms of anomalous growth. Joachimsthal¹⁷ found in some lilliputians that he examined that the bone formation was delayed, and the condition of the discs and of the bone generally was strictly comparable to that found in the child, although the subjects were in the neighborhood of thirty years of age. Hofmeister¹⁸ also in cretinism found that the epiphyseal discs persisted for a long time, and that the epiphyseal ends of the bones grew slowly. In chondrodystrophia foetalis an ingrowth of periosteum has in some cases been observed between the disc and the end of the bone. The significance of this is not quite clear. In acromegaly, on the contrary, where the increase of size of the bones, still at the distal ends, is in breadth and thickness, rather than in length, there is complete union or synostosis of the epiphyses. With regard to giants we unfortunately have no information on this point, but I think we may fairly infer that, while growth is in excess, epiphyseal synostosis is delayed. The importance of the condition of the epiphyseal discs in modifying the extent and the direction of the growth is also prettily illustrated by the observation of Lorain, who found in some cases of dwarfism premature ossification and union of the epiphyses.

In our discussion of growth and its anomalies so far we have contented ourselves mainly with freeing the subject from entanglements, and so to speak preparing the ground for action. When we come to consider the more remote factors concerned in the question of growth we find ourselves in a much more difficult position. As we do not know what life is we can apprehend its methods and its manifestations only in an imperfect way. Many of our ideas, therefore, have to be based upon inference rather than direct proof.

The part played by heredity in gigantism, as in other anomalies of development, is of considerable interest and importance. This factor might be expected to be more prominent in cases of congenital gigantism, and as a matter of fact it is so, but its influence cannot be overlooked in the other forms. It is a matter of common observation that parents transmit their tendencies and peculiarities to their offspring, and moreover these peculiarities may be traced through several generations; in fact they may become familial or racial characteristics. This law manifests itself in many ways, in the size and configuration of the body, in the color of the skin, the mentality, habits, the susceptibility to disease, and in many minor traits. The peculiarities derived from the paternal and maternal sides may be of such a nature as to neutralize one another, or again they may unite their forces to produce an exaggerated effect, an effect so pronounced as to be marked at once as an anomaly. With regard more par-

ticularly to gigantism, we do not meet with the anomaly as a racial characteristic at the present day. At most we can say that some races tend to be tall and large, while others are small or even dwarfed. If the ancient accounts are to be believed giant peoples have, however, existed. Whatever stress we may lay upon this, at the present time gigantism is an sporadic affection. It is a suggestive and striking fact that once the tendency toward gigantism is acquired it is apt to crop out at various times in the same lineal descent, exemplifying the law of atavism. Again it may often be noted that more than one of the children of the same household will be affected. A number of cases might be quoted to illustrate these points. In Dickinson's case (*loc. cit.*) mentioned above, a woman bore three children who weighed nine, twenty, and sixteen pounds respectively. Fuchs' case (*loc. cit.*) was a IX-para. Her sixth child weight 6 kgm., her eighth 6.1, and her ninth 7.55. Her other children had also been heavy. The same thing has been noted by other observers. Goulart refers to a Polish giant who was exhibited in Paris in 1571, and was so tall that in a lofty room he could touch the ceiling with his head. He was married and had a son who promised to be as tall as he was.

James Toller, exhibited in London in 1815, was seven feet nine inches high. His parents were of normal build, but he had two sisters of gigantic stature. Louis Frenz, a French giant, who was born in 1800, and measured seven feet six, had two sisters as tall as he was and one brother who was much larger. The family history of Robert Hales, "the Norfolk giant," is also quite striking. His father was six feet and a half, his mother six feet, in height. One of his ancestors, who lived in the reign of Henry VIII., measured eight feet eight inches. Hales had five sisters who averaged six feet three and four brothers who averaged six feet six. The tallest of the sisters died at the age of twenty, measuring seven feet two. Captain and Mrs. Bates, both over seven feet, had a child which is almost the largest on record. One of the sisters of Chang, the Chinese giant, was even taller than he was, measuring eight feet four.

These facts suggest that this anomaly of growth is due to peculiarities inherent in the germinal cells of the parents. This view is supported by the observations of Engel-Reimers,¹⁹ who has emphasized the fact that excessive muscular development, the so-called "athletic habitus," appears to be due to an abnormal hereditary predisposition and not to hypertrophy from functional overactivity. This is well borne out by the physical condition in new-born giant children. They frequently present the athletic habit. The head is about the size of that of the normal infant, but the trunk is massive. Now this hypertrophy, if we can call it such, is clearly not due to mechanical work nor to compensation, nor to the other ordinary causes of overgrowth. It must be due to some disturbance of nutrition. The relative importance to be attached to peculiarities of the male and female germ cells is still in doubt, for in the recorded cases we rarely have any statement as to the physical condition and development of the father. From the instances cited it is evident that both germinal elements may play a part. But it is equally evident that some idiosyncrasy in the maternal organism alone is sufficient to produce the result. In Fuchs' case, for instance, the father is noted as having been in a poor state of nutrition. This has led Werth to suggest that the tendency to produce large children is due to an inherent peculiarity of the ovum, possibly to its large size. However this may be, we have sufficient evidence to show that large size on the part of one or both parents is not necessary to produce the result in question. Yet it seems probable that physical superiority in the mother, if not in height, at least in physical constitution and nutrition, is an important etiological factor. In 178 cases of large and giant children collated by Fuchs, 166 mothers are noted as being of more than usually strong physical development and nutrition. The remaining 12 were weakly, but in no case did their children exceed 4.36 kgm. in weight, a size which, according to our adopted standard, cannot be re-

garded as gigantic. In view of this fact we see that the influence of maternal development and nutrition assumes considerable importance. Exceptions to this, however, occur. In a case cited by Dubois, a woman with extensive tuberculosis gave birth to a child weighing 6.336 kgm., and another with severe diabetes had a child of thirteen and a half pounds. Two possibilities must evidently be considered in this connection, a primary peculiarity of the ovum or sperm cell, or both, and a condition of increased intra-uterine nutrition. The influence of peculiarities of the primitive germinal cells would perhaps be best illustrated by instances of the atavistic manifestation of gigantism, or in those cases, like that of Dubois, in which the maternal organism was conspicuously weak, for in the latter case increased intra-uterine nutrition could obviously play no part. Some of the forms of minor terata, such as polydactylism, are no doubt also of this nature. Polydactylism has been known to run through a family for three, four, or even five generations, being eradicated only in process of time by marriage with normal persons. Curiously enough polydactylism has been found associated both with dwarfism and with gigantism. It has been thought by some that mothers in whom the function of menstruation was established early were more likely to have larger children than others, apparently on the theory that such persons were possessed of greater reproductive energy. Negri on the basis of 333 observations has stated that the children of mothers who began to menstruate early were both larger and heavier than the offspring of those whose menstruation was late in coming on. This has not been confirmed, however, by other observers. The point can probably not be decided until more studies on the subject are forthcoming. It is, nevertheless, true, so far as the records go, that large children are more likely to be borne by those who are at the height of reproductive activity and who have had previous children. In elucidation of this point we may perhaps quote Fuchs' statistics. In 176 of his cases, already referred to, the age was ascertained. These were divided as follows: I. Under twenty years, 5; of this number 5 were primiparæ. II. Twenty to twenty-five years, 72; of this number 18 were primiparæ. III. Twenty-six to thirty-five years, 75; of this number 2 were primiparæ. IV. Thirty-six to forty-eight years, 24; of this number none were primiparæ.

Between the ages of twenty and thirty-five, the years of the greatest sexual activity, the number of large children was greatest. Now, taking the third class, we find that only 2.6 per cent. were primiparæ. If these results be compared with those obtained from a series of 1,000 normal births, in 342 of which the mothers belonged to the third age period, it will be found that there were 57 primiparæ, a proportion of 16.9 per cent. This corroborates the observation made a little while ago that certain women show a tendency to produce large children, or in other words that the tendency once manifested tends to perpetuate itself.

Intra-uterine nutrition is undoubtedly a factor of considerable importance. In the article on *Dwarfism* or *Nanosomia* in this volume the rôle played by intra-uterine malnutrition in the causation of inhibited growth is dealt with at some length. Here syphilis, alcoholism, and tuberculosis, together with lesions resulting in interference with the free circulation of blood through the placenta, are of importance. Conversely, an overplus of nutritive energy might be expected to produce its effect upon the fruit. In this connection we have to take into account the condition and surroundings of the mother during pregnancy. Pinard (cited by Bouchacourt²⁰) compared the average weight of 500 new-born children whose mothers had worked up to the time of delivery with that of the same number of children whose mothers had rested during the later weeks of pregnancy. He found a notable superiority in weight and nourishment in the offspring of the latter class. In a similar inquiry Bachimont (cited by Bouchacourt) in a series of 4,445 observations found the excess in weight for the latter class of children to be, on the average, 300 gm. In this

particular it should be remarked that very large children lead perforce to a condition of complete inactivity and inertia on the part of the women pregnant with them. This of course means rest which tends to increase in turn the size of the child. Thus a vicious circle is induced. The importance of intra-uterine nutrition in modifying the weight of the fruit is well illustrated by the good effect of dieting in those cases in which a woman has either a tendency to produce large children or else has some contraction of the pelvis. By this procedure it has been found possible to deliver such a mother of a living child.

Some attention had been directed to the subject of prolonged gestation and its effect in producing large children. The statistics seem to show that this factor has a certain amount of importance, but it is probably effective only when combined with other causes. It does not seem to me, however, that it is justifiable to place cases of this kind in the same category with giant growth. If, for example, a child is retained within the uterus for three hundred and eight days instead of two hundred and eighty, it is practically in the same position as an infant one month old, due allowance being made for differences between intra-uterine and extra-uterine modes of nourishment. Such a child would derive no permanent advantage from its prolonged retention within the uterus, and would probably develop later much as other children do. In other words, the vitium of excessive growth is not inherent. Unfortunately many of these points we have touched upon cannot be verified by any large series of observations. Gigantism in the first place is much rarer than dwarfism. Then the majority of giant children are still-born. Even those cases in which giant growth manifests itself later in life are beset with difficulties. The number of carefully made studies is not great and prolonged observation is rarely possible, not only from the fact that giants are apt to die early, but on account of their nomadic kind of life.

In dealing with the question of heredity we have adduced numerous facts to show its importance in the causation of anomalous forms of growth. The influence of this factor, while perhaps more direct and striking in the case of giant births, is nevertheless, as we have shown, to be taken into account in the post-natal forms. But besides this we have to consider the bearing of internal metabolism on the subject. The more recent work done on cretinism and the results of the experimental removal of the thyroid gland have taught us that a condition of athyroidia, which undoubtedly acts by perverting the metabolic processes of the organism involved, has a profound effect on the function of growth and development, namely, in the direction of inhibition. In that other most remarkable perversion of growth, acromegaly, where there are enlargement and deformity of the body, or excessive growth, gross lesions of the pituitary body have been found. Disorders of internal secretion obviously are of some importance.

The general resemblance between acromegaly and gigantism has led to the promulgation of the view that the two conditions are one and the same thing, and the controversy over this point has waxed hot and heavy. Without being prejudiced on either side, I think that the careful observer cannot fail to be impressed with the parallelism which exists between the two affections. Brissaud and Meige have been the chief exponents of the identity theory, while Marie, who first differentiated acromegaly as a disease entity, though he has somewhat receded from his first position that acromegaly and gigantism are entirely distinct, has not been entirely convinced by the arguments adduced against his position.

Marie in his first studies on acromegaly summarized it as a peculiar affection, characterized by a massive hypertrophy of the bones of the extremities and the extremities of the bones. He admitted that a number of cases had been confounded with gigantism, for the reason that attention had been directed to the excessive height to the exclusion of the less obtrusive signs, while the disease in

those of normal stature had been overlooked. Shortly after, Guinon,²² following Marie's lead, took the same position that the two affections were essentially different, on the ground that as our knowledge had increased it had to be recognized that persons with acromegaly were by no means always gigantic; in fact they were often below the average height, and again that the configuration of the body was different in both. The various parts of the face and limbs preserved their normal proportions in gigantism while the course of the two affections was different. Guinon even went so far as to state that gigantism is as a rule simply an exaggeration of a normal process, while acromegaly is a disease. It is undoubtedly a fact that typical, or what we might call "text-book" cases of the two affections present an entirely different picture. There have been some giants that presented none of the morphological characteristics of acromegaly, as there have been persons with acromegaly that were not giants. It ought to be unnecessary, however, to point out that even the best-known diseases present at times wide variations from the type. The case of typhoid fever, for instance, need only be mentioned. This being the case it by no means follows that two diseases, at first sight dissimilar, have nothing in common, or even that they are not due to the same cause. The point may be further illustrated by the history of cretinism and myxedema. At one time it was believed that these conditions, which in many ways are so unlike one another, at least to superficial examination, were distinct diseases. More careful study has, however, shown that both depend on a condition of athyroidism, and few will be found now to deny that cretinism and myxedema are one and the same thing. The modifying factor has been found to be the age and the concomitant stage of development of the affected individual. If athyroidism becomes manifest in infancy before the bony skeleton is consolidated we get cretinism. If it develops later, when the bony skeleton is complete, the soft parts only are involved and we get myxedema. It is unsafe then to conclude that one and the same cause may not at times produce widely different results. In other words, the trophogenic function of the individual may be so predominant that it is sufficient to alter a morbid state almost beyond recognition. It has already been pointed out that the normal process of growth manifests itself most strongly at the epiphyseal ends of the long bones, and that increase in length of the bones is possible only so long as the epiphyseal discs remain ununited, save by the softer structures, to the diaphyses. Similarly, the abnormal processes of growth, such as dwarfism and gigantism, manifest themselves at the same points. Deficient vegetative energy in early life will result in stunting the growth of the long bones, and the same thing will happen if the epiphyseal cartilages are prematurely ossified. Excessive vegetative power during adolescence results in increase in height; if synostosis of the epiphyses has taken place, as occurs in adult life, then it is conceivable that, increase in length being impossible, increase in breadth and thickness must occur. Do, then, acromegaly and gigantism bear to one another a relationship similar to that existing between myxedema and cretinism? Many facts point in this direction. Numerous observations have shown that acromegaly frequently supervenes in gigantism. Surmont²³ in 1890 reported a case of acromegaly in a girl of eighteen, in whom the symptoms were preceded by a notable increase in the size of the body. The enlargement was generalized, but most marked at the extremities. Byrom Bramwell²⁴ mentions the case of a giantess who was attacked by acromegaly. Swanzy²⁵ also demonstrated the lesions of acromegaly on the skeleton of McGrath, the Irish giant, before the Royal Academy of Medicine of Ireland. Shattock²⁷ believed the skull of O'Brien to be acromegalic. In 1893 Dana¹⁶ published two cases of acromegaly associated with gigantism, and he remarks that the coincidence of the two affections is more common than has usually been supposed. He further mentions a great many symptoms which they have in common, and brings out the most im-

portant point, viz., that out of twelve autopsies on giants the pituitary body was enlarged in ten. In the case of "Adna," a French giantess, who died at the age of twenty-one, measuring six feet eight and a half inches, Hutchinson states²⁸ that the face and extremities presented the well-known features of acromegaly. At the autopsy the pituitary gland was found to be considerably enlarged. A striking case, also, is reported by Brissaud and Meige.²¹ J. P. Mazas, the giant of Montastruc, began to grow rapidly when thirteen years of age, and became very strong and robust. At twenty-one years he was 212 cm. high, eventually reaching 220 cm. At the age of thirty-seven he experienced a severe pain in the back, which he attributed to lifting a heavy weight. Deformity of the back set in and his height began to diminish. He gradually developed enlargement of the face and extremities, headache, weakness, intellectual and sexual torpor, and all the classic symptoms of acromegaly. Sternberg,²⁹ also, in an elaborate paper on the subject found signs of acromegaly in forty two per cent. of giants. More recently Walker³⁰ reported an instance of acromegaly in a boy, who began to grow rapidly when six years old, and who at sixteen was six feet five and a third inches high, and weighed two hundred and forty-five pounds. Bonardi¹⁵ refers to the case, already mentioned in another connection, of a boy who at the age of fifteen had the size and development of an adult male. When twenty-two years old he began to suffer from pains in the head and nausea. Soon after, general weakness set in, with enlargement of the hands, feet, maxillæ, and tongue. At twenty-nine he was 194 cm. high and was typically acromegalic. By a careful study of the recorded cases we see, therefore, that a considerable degree of parallelism exists between the two affections. Perhaps the most important points are to be noted in the skeleton.

The typical features in acromegaly are enlargement of the bones of the face and extremities. The hands are "spade-like," and the fingers rounded. In severer cases all the bones of the body become involved. The thorax enlarges and the trunk becomes scoliotic, so that a loss of height takes place. There exist, however, lesser disturbances of bone formation that are difficult to class, being on the border line between gigantism and acromegaly. In such cases the dystrophic disturbance is confined to one or more parts of a member, or to two members symmetrically. Such malformations may be both congenital and acquired. Of such a nature are those cases in which there is deformity of the face without enlargement of the hands. Chauffard³¹ reports a case in which a man of thirty-two presented the features of prognathism, macroglossia, prominence of the external occipital protuberance, headache, anæmia, loss of vision to the right, and slight kyphosis. Some of the anomalies, then, that are to be found in acromegaly may be found without the other features of the disease in certain forms of developmental dystrophy, and may arouse a suspicion as to the acromegalic nature of the case. When such peculiarities are met with in giants we may properly inquire whether they are the stigmata of acromegaly, or whether they merely simulate that disease. In giants thickenings of the extremities of the long bones, hyperostoses, and exostoses have been noted, identical with those that for so long have been regarded as characteristic of acromegaly. Deformities of the knees, which as Osborne, Middleton, Schultze, Hirschmann, and Roswell Park have shown, are fairly common in acromegaly, have also been met with in gigantism. Lucas Championnière in 1899 demonstrated to the Academy of Medicine a giant, aged twenty-seven, who measured 203 cm., and presented an extreme genu valgum. This peculiarity has a double interest in that it affords a link between acromegaly and gigantism, and also connects the latter with infantilism. The curvature of the spine and the rounded thorax, so often found in acromegaly, have been found in gigantism, but our information is defective in this regard.

With respect to muscular power great variations may occur both in gigantism and in acromegaly. Several ob-

servers, notably Meige, Dallemagne, Virchow, P. Marie, Souza-Leite, Bourneville, and Regnault, have noted acromegaly developing in persons of exceptional muscular vigor. Some giants, like the Emperor Maximin and the Countess Lodoïska, have been of great strength. This, however, seems to be the exception. Geoffroy Saint-Hilaire states that giants are "without activity, without energy, slow in their movements, avoiding work, quickly fatigued; in a word, feeble in body as well as in mind." Amyasthenia and general weakness are by no means uncommon in acromegaly.

As is well recognized there is a characteristic facies in acromegaly. Meige is our authority for the statement that giants who are still in the period of growth present no special facial peculiarities. In those who have ceased to grow there is an exaggerated development of the face as compared with the cranium. We can sometimes note that the malar eminences are prominent, the lower jaw enlarged, and the angle widened, while the lips are thick. The beard is often thin, the skin thick and dark, the pupils dull, and the whole appearance lacks vivacity. These peculiarities are by no means invariable in giants, nor indeed are they so in acromegaly. We have to allow here as elsewhere for individual variations. In fact, we may perhaps with Hoffmann distinguish between acromegaly of the soft parts and acromegaly of the bones.³² Meige is, on the whole, inclined to believe that the face in giants at one time approaches the acromegalic type, at another the infantile.

Vascular disturbances have been found in both acromegaly and gigantism. In both the pulse is slow, the circulation sluggish, and there may be varices.

Pains in the head have been found in both affections. Pains also in the limbs, vertebral column, and the viscera, have been met with in about half the recorded cases of acromegaly. These may simply amount to a sense of fatigue or lameness, but may be actually articular, muscular, or neuralgic. It is a popular belief that rapid growth in children is associated with "growing pains," and it is interesting that the same thing has often been noted in giants. In the case of McGrath, for instance, the increase in growth was associated with the most violent pains in the limbs.

Visual disorders have been met with both in acromegaly and in gigantism. In acromegaly, at least, they have been found to be dependent on the presence of a tumor of the pituitary body.

Polydipsia, polyphagia, and abundant sweating have been observed in both affections. Polyuria and glycosuria are occasionally met with in acromegaly and in giants who become acromegalic.

In both gigantism and acromegaly there is often to be noted sexual frigidity in the male, and amenorrhœa in the female.

To sum up, the two affections frequently have the following symptoms in common: asthenia in the widest sense of the term; muscular weakness, notwithstanding the absence of atrophy; intellectual degradation; melancholy; headache; diminution of sexual desire in the male; amenorrhœa in the female; alterations in the skin; varices. Lastly, of a great importance, lesions of the pituitary gland have been found in a majority of both affections.

Further, the influence of heredity is marked in acromegaly as in gigantism, and indeed it is not uncommon in probing into the family history to find that acromegaly and gigantism are liable to be met with in the same family. Schwoner, for instance, records³³ a case of acromegaly in a woman of forty-five, whose mother had become acromegalic at fifty. All the members of the family on both sides of the house are noted as having been of great stature. Lackey³⁴ describes a case of acromegaly in a negro who reached the extraordinary height of eight feet six. His grandfather is said to have been a giant.

In view of the facts outlined above, Brissaud and Meige would discover a general principle underlying the dystrophic disturbances that result in excess. Growth at all periods of life tends to be manifested most conspicuously

at the epiphyseal ends of the long bones. The effect produced is controlled by the age of the patient, or, in other words, by his vegetative capacity and the condition of his epiphyseal cartilages. The same pathological process which in the young gives rise to gigantism will, if continued after the normal period of growth in stature is passed, cause acromegaly. If it becomes operative in later youth, when the bones are largely formed but growth is not complete, we get a combination of acromegaly with gigantism. This is to some extent corroborated by the lesions in acromegaly, for, as Marie himself has shown, in cases of acromegaly that begin early in life, the extremities are more elongated than thickened, and are quite unlike the spade-like extremities characteristic of the disease as it occurs in later life. Further, it may be safely stated that acromegaly has never preceded gigantism, while acromegaly has succeeded gigantism in almost half the cases. Brissaud and Meige, however, would go further. They see the same principle at work in the chronic rheumatism so-called of the aged, in rheumatoid arthritis and gout; in youth, in gigantism; in adult life, in acromegaly; in old age, in nodes. They support this by an observation made by Gaston and Brouardel³⁵ with the *x*-rays on a woman of sixty, who began to show signs of acromegaly at forty-two after the menopause. The disease was slowly progressive, and thickenings in the form of nodules could be made out on the epiphyseal lines.

Without endorsing the rather startling proposition put forth by Brissaud and Meige, that "acromegaly is gigantism of the adult; gigantism is acromegaly of adolescence," it seems to me that the unprejudiced observer cannot fairly deny that they have proved their main contention. There is undoubtedly a close connection between acromegaly and gigantism, and the two affections in a large proportion of cases merge gradually one into the other. Gigantism frequently becomes acromegaly. But how about the other fifty-eight per cent. of cases of gigantism that present no signs of acromegaly? Are these, too, of the same nature, or are they in a different category? It is not impossible nor even unlikely that some of them are due to the same factors as acromegaly, as it is ordinarily understood. Here we have to consider the natural variations of disease. Diseases do not invariably run their course. They may become ameliorated or may be aborted. Acromegaly itself may present an extremely slow progression, and in fact may cease to advance. A fatal termination does not always occur. It may well be, therefore, that acromegaly beginning in early adolescence may progress only sufficiently far to produce increase in length of bone without the other signs supervening. It may be recalled in this connection that the majority of giants die early. Byrne, the Irish giant, died at twenty-two; James Toller at twenty-four; the "Queen of the Amazons" at about twenty. This may perhaps be the effect of the acuteness of their malady, but in many cases it is due to intercurrent disease, as the resisting power of giants is notoriously low. However this may be, it is plain that many giants die before the period of age incidence of acromegaly, that is to say, before adolescence is completed. We cannot therefore say that they would not have become acromegalic had they lived. It is possible, therefore, that the majority of the cases of gigantism are dependent on the same pathological factors as acromegaly.

There has been considerable debate as to the exact nature of the cause or causes at work in acromegaly. Klebs advanced the theory that acromegaly is due to angiomas. Vascular lesions are undoubtedly present both in acromegaly and in gigantism. Witness the arteriosclerosis, the varices, the vaso-motor ataxia, and the hypertrophy of vessels to adjust themselves to the increased size of the body. But there is no proof of any new formation of vessels. Lancereaux, again, has suggested that it is a trophoneurosis. The enlargement of the hands and the disturbed innervation met with in syringomyelia might suggest this. This view is not, however, supported by any known facts. von Strümpell has thought that it is a

congenital dystrophy. The majority of observers are, I think, practically agreed that acromegaly is dependent on some gross lesion of the pituitary body, in the form of hypertrophy, cystic growth, adenoma, or other tumor growth. Osborne believes that gigantism in its perfect development is due to a normal hypertrophy of the pituitary gland; that is, to a hypersecretion occurring at the age of puberty or age of general or symmetrical body growth and development. He believes further that gigantism will remain such as long as the pituitary body is in normal hypertrophy, but that these cases of gigantism will assume later an acromegalic type, if, as is often the case, the pituitary body begins to take on pathological conditions. In other words, he believes that an excess of normal secretion from the pituitary gland is the cause of gigantism, while perverted secretion is the cause of acromegaly. This conception is very different from that of Brissaud and Meige, in that it attributes the lesions, which we call gigantism and acromegaly, to two distinct and separate states of the pituitary function. Brissaud and Meige's view implies that the same condition of the pituitary function is at work in both cases, any differences in the results produced being attributable to the age period at which the process begins. We know so little of the nature of the normal function of the pituitary body, and indeed of its disturbances, that it would be hazardous as yet to express an opinion either way. For my part I cannot understand the term "normal hypertrophy," as applied to the pituitary. We have, it is true, what might be called normal or physiological hypertrophy in the case of the pregnant uterus and possibly in the functioning breast, yet this is but a temporary condition and is paralysed, so far as I know, nowhere else in the body. Gigantism is an abnormal condition, and to my mind cannot be explained on the basis of a "normal" hypertrophy. It may, however, be true that it is due to an excess of pituitary secretion. But if this can produce increase in the length of bone, why is it not also competent to produce increase in thickness of bone? One seems as likely as the other. Whether acromegaly is due to a hypersecretion on the part of the pituitary, as many seem to think, or to a diminution of the secretion, or again to a perverted secretion, cannot, however, be regarded as settled. Tumors, cysts, and plain hypertrophy of the pituitary have been found in the majority of autopsies on acromegalic cases, and tumors of the pituitary in acromegalic giants (Buday u. Jancto,³⁸ Oestreich u. Slawyk³⁷). Possibly simple hypertrophy or adenomatous growths may imply oversecretion; but cysts or destructive tumors, like the sarcomata that are so frequently found, might be interpreted as lessening the amount of secretion. Conversely, tumors of the pituitary may exist without signs of acromegaly, as in two cases that have come under my own observation. Both were malignant (one sarcoma and one endothelioma). Here we must assume either that the pituitary was able to furnish the proper amount and kind of secretion, or else that compensation had taken place. We are realizing more and more the importance of the principle of compensation in regard to the body metabolism. We see, for instance, that there is a close relationship between the thyroid gland and the pituitary body. In acromegaly the thyroid gland has been found hypertrophied, cystic, or atrophic, and the disease may be complicated by the symptoms of exophthalmic goitre or myxedema. In this connection may be mentioned a most remarkable case, reported by Pope and Clarke,³⁸ in which a man suffering from acromegaly had a daughter with myxedema and an atrophied thyroid, who at the age of twenty presented the physical and mental characters of a child of five. Ponfick, Hymanson, Pineles, and Green, in particular, have noted the association of acromegaly with myxedema, and Murray³⁹ its combination with exophthalmic goitre. Conversely, the pituitary has been found enlarged in cases in which the thyroid was atrophied (Boyce and Beadles⁴⁰), and when this occurs it seems to prevent at least the immediate results of thyroid defect, namely, cretinism or myxedema. In the

article on *Dwarfism*, by the present writer, in this volume, the relationship of thyroid dystrophy to that other anomaly of growth allied to gigantism, namely, dwarfism, is dealt with at length, and it is there shown how the condition of athyroidia may result in inhibited growth and genital insufficiency. The stigmata of infantilism in acromegaly and in gigantism have suggested the possibility of disorder of the thyroid in these affections, and there have not been wanting those who would attribute acromegaly to thyroid dystrophy. Facts, however, do not favor this view.

Genital hypoplasia and malformation, as well as genital inadequacy, have been met with in dwarfism, cretinism, infantilism, gigantism, and acromegaly, and this leads us to discuss in how far disorders of the sexual apparatus are responsible for anomalies of growth. In this connection a number of interesting facts may be adduced. The sexual languor, as it might be termed, found in both acromegaly, and gigantism, has been referred to. Garnier and Santenise⁴¹ have observed a case of gigantism associated with feminism, cryptorchidism, and polysarcia. Thoma⁴² mentions having met with defective formation of the genital organs in a case of hemihypertrophy. In acromegaly, as soon as the changes in the bones become manifest, the secondary sexual attributes are changed. In the male the hair becomes scanty, while in the female hair is apt to grow on the face much as it does after the menopause or in ovarian disorders. The larynx hypertrophies and the voice deepens. Infantilism and hypoplasia of the genital organs have also been observed in cases of tumor growth in the pituitary in the absence of signs of acromegaly. Some years ago I performed an autopsy on a woman about thirty years of age who had a perithelial sarcoma of the pituitary without signs of acromegaly, in whom the genital organs were markedly undeveloped. Babinski also reported to the Neurological Society of Paris (June 7th, 1900) the case of a girl of seventeen, who presented the signs of infantilism, amenorrhœa, abundant fat, scantiness of hair, but without acromegaly. She developed pains in the head with disordered vision, and epileptiform convulsions. After death it was discovered that she had a tumor of the pituitary. It is clear then that there is some relationship between lesions of the pituitary and thyroid glands and genital disturbances. What, then, is the primary disorder which leads to such extraordinary anomalies of growth and development? Breton and Michaut⁴³ have suggested that there is a trophic deviation of the genital activity to the bone marrow so that the medullary bone-forming function preserves its activity indefinitely. The cessation of genital activity would lead to acromegaly. This view is somewhat similar to that promulgated previously by Freund, Klebs, and Verstraeten, who held that there is a disturbance of the evolution of the genital function. If genital evolution is in excess we get gigantism and acromegaly; if defective, we get infantilism and dwarf growth. It is, of course, well recognized that with the onset of puberty the efflorescence of the sexual characteristics is coincident with increased growth and development of the body as a whole. The operation of castration has been observed to exert a notable effect on the stature of the body as well as in inhibiting the development of the secondary sexual peculiarities. In eunuchs the height is often extreme. This is due chiefly to a disproportionate increase in the length of the legs. Lortet has confirmed this statement by an examination of the skeleton of an Egyptian eunuch 196 cm. high. In castrated animals, the capon and the ox, the same increased growth of the lower or hind extremities is to be observed. Silva⁴⁴ has further recorded a curious observation in a youth who was normal until the age of thirteen. The testes then remained atrophic and when about twenty he began to grow rapidly, eventually manifesting some enlargement of the head and extremities, muscular weakness, anosmia, slight scoliosis, to such a degree as to suggest acromegaly.

While such facts as those just mentioned are suggestive of some relationship between genital insufficiency

and disorders of growth and nutrition, to my mind the evidence is not strong enough to induce us to accept the view that deficiency of the genital organs is the cause of these disorders. Two-thirds of the cases of acromegaly develop after puberty is practically reached. The loss of sexual power in the male is gradual and progresses *pari passu* with the extension of the disease itself. In the female, too, while amenorrhœa is a frequent and often the first symptom of the disease, it is not invariable. Again genital hypoplasia and other signs of infantilism are often present in dwarfs, and the argument might be applied with equal force to explain dwarfism. The same cause could hardly produce at one time dwarfism and at another gigantism. Moreover, while genital hypoplasia has been often observed in cases of thyroid atrophy and gross lesions of the pituitary body, so far as is known castration does not produce a converse effect on these particular organs. While, then, genital hypoplasia undoubtedly plays some rôle in osteogenesis, it seems to be quite a subordinate one, and appears to be inadequate to explain the more marked aberrations from the normal path of development. The functions of the thyroid gland, the pituitary body, and the sexual organs are, however, no doubt correlated, and it is probable that the normal course of growth and development is dependent on a certain balance of power exerted by these glands. Of what nature is this correlation we are to a great extent in the dark. It is generally believed that the glands mentioned produce internal secretions that are essential to the normal course of the metabolic processes. The evidence in favor of this is less strong in the case of the sexual organs (testes and ovaries) than for the other organs. It may be inferred that while the metabolic processes referred to are vital in nature, they are inextricably associated with chemical transformations. The importance of chemical substances in the growth of the organism is well illustrated by the experimental work of Wegner, Maas, and Gies.^{45, 46, 47} Wegner proved that by feeding rabbits with minute doses of phosphorus for a prolonged period he could get a marked increase in the formation of bone at the epiphyseal sutures of the long bones. The same thing has been found to occur with arsenic. Observations upon the nature of the metabolism in giants are hitherto lacking, but we have considerable evidence to show that in acromegaly metabolism is disordered. There appears to be a tendency to an overproduction of lime salts in acromegaly. Deposits of lime have been found in various parts of the body, especially in the pituitary, the thyroid, and the vessels (arteriosclerosis). Ossiform infiltration of the dura mater has been observed. Von Morawski⁴⁸ has also demonstrated a tendency to the retention of lime and phosphorus in the system in cases of acromegaly. Not only then is there an increased deposit of lime at the extremities of the bones, but also in widely distant parts of the body.

We are, I think, led to the inevitable conclusion that gigantism, like acromegaly, is very often a disorder of development brought about by abnormal metabolic processes. We must also admit that a large proportion of cases of gigantism are etiologically the same thing as acromegaly, and that an additional but uncertain number are probably abortive acromegaly (acromégalie fruste). One consideration must, however, be by no means overlooked in any discussion of the question of internal secretion. The doctrine of internal secretion as at present understood implies the existence of certain substances in the body upon which the secretion of the glands in question may act. Now the gland, thyroid or hypophysis, may be totally unable to perform the duties required of it, owing to some lesion, or it may be only relatively so. In either case similar symptoms would arise. This doctrine of relative inadequacy has been advanced by Prof. J. G. Adami,⁴⁹ and has by no means attracted the attention it deserves. On the one hand, relative inadequacy of a gland will set in as soon as its reserve power has been exhausted, and may increase until it becomes absolute. On the other hand, there may be an excess of the substances upon which the internal

secretion is supposed to act. Therefore it is quite possible that certain forms of developmental disorder may be due to relative inadequacy on the part of some of the important glands, that, as we have seen, are competent to modify nutritive processes. In the case of gigantism, relative inadequacy of the pituitary, or it may be a relative overadequacy, short of producing the regular symptoms of acromegaly, might influence growth so as to bring about excess.

However this may be, and the deduction is alluring, there still remains some small proportion of cases of gigantism which cannot be explained on any of these theories. Such are the cases in which in addition to excessive height there is great strength with perfect proportion. Here there can be no question of disease in the ordinary acceptance of the term. Such giants are examples of the so-called "athletic" habit of body, and are strictly comparable to the giant infants before referred to. They represent the structure of the human body carried to its highest point. They may be regarded as examples of *true* or *essential* gigantism. Infantilism and pituitary dyscrasia cannot explain them. Rather are they to be referred to peculiarities inherent in the germinal cells of the progenitors. This view is supported by the fact that certain anomalies, for example polydactyly, malformations of the genital organs, and congenital hydrocele, are apt to be associated with the increase in size and weight. *Albert George Nicholls.*

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GLANDULAR FEVER.—*Synonyms:* Drüsenfieber, fièvre ganglionnaire.

DEFINITION.—Glandular fever is an acute infectious disease of childhood, characterized by sudden onset, fever, swelling of the cervical lymphatic glands, and constipation; but there is no exanthem. It is probably contagious.

ETIOLOGY.—The cause of the disease is unknown. It has been suggested that the tonsil or pharynx may be the portal of entry for the infectious agent, whatever it may be; but there seems to be no discoverable local lesion. Another theory is that the infection finds entrance through the intestines; and some color is lent to this theory by the suggestion that it might possibly explain the fact that the left cervical glands are the ones chiefly affected, since the infection might spread to them from the thoracic duct. It is essentially a disease of childhood, most, but not all, of the cases occurring before the tenth year. A case of glandular fever occurring in a young lady twenty years of age was reported by Mayer, of New York, in the *Medical Record* of August 11th, 1900. The winter months of the year seem to be the most likely time for the disease to be contracted; and previous diseases, general malnutrition, and lowered vitality act as predisposing causes. Sex seems to have no bearing upon the etiology.

The first account of the disease is probably that by Filatow, of Moscow, in 1885. Four years later E. Pfeiffer described the disease, and drew attention to the fact that it was apt to occur in circumscribed epidemics; he also noted that where one child in a family suffered from the disease, the others were very liable to suffer too. In December, 1896, Park West published an account of an epidemic in eastern Ohio from 1893 to 1896. The cases were ninety-six in number, and occurred in forty-three families. They were all in the practice of Dr. F. A. Korell of Businessburg, O., and were reported by him in a paper read before the Belmont County (Ohio) Medical Society on April 27th, 1896.

This is probably the largest epidemic yet noted, and West's article, besides giving statistical tables, provides an extensive bibliography.

SYMPTOMS AND COURSE OF THE DISEASE.—The period of incubation probably lasts from about five to eight or ten days; and during this period there are no symptoms. The onset is sudden, and is accompanied by pain and tenderness in the neck, both of which are made worse by moving the head. Fever is an early symptom, and is apt to be of the remittent type; as a rule it is only of moderate degree, the body-temperature running from 101° to 103° F., occasionally to 104° F. There is no rash, but the face may be flushed in the early stage of the disease. Nausea, anorexia, constipation, and abdominal pain are apt to occur. Inflammation of the throat and pharynx are present; and dysphagia is marked. The lymphatic glands are enlarged and some of them can be easily palpated; this is particularly noticeable in the cervical and carotid regions just below and near the anterior border of the sterno-cleido-mastoid muscle. The swollen glands with the accompanying pain and tenderness are generally found on the left side.

The posterior cervical, axillary, and inguinal glands may become similarly involved. The mesenteric glands may also be affected; and abdominal tenderness, with enlargement of the spleen and the liver, is present. The fever abates as the adenitis reaches its height, and the latter may last for a couple of weeks while the fever remains only a few days. In the Ohio epidemic the average duration of the disease was sixteen days. The most serious complication is nephritis. Suppuration of the glands is rare, and is treated by incision and drainage.

"In two cases in which the general symptoms were severe, Moussous observed the onset, on the third or

fourth day of illness, of cough which occurred in paroxysms ending in vomiting, but without the characteristic whoop or glairy expectoration of whooping-cough. This appears to indicate that the tracheo-bronchial glands may be enlarged during the course of the illness" (Dawson Williams).

PATHOLOGY.—As the disease is so very seldom fatal, opportunities for the study of its pathology are correspondingly rare. In Mayer's case, referred to above, the red blood cells were pale, and showed a deficiency of hæmoglobin; the proportion of red to white cells was normal, but the eosinophiles were increased both in size and number. In addition to what is said above under Etiology and Symptoms, we add the following from the article on "Glandular Fever," by Dawson Williams, in the "Twentieth Century Practice of Medicine."

"Cantlie became familiar in Hong-Kong in 1891, and therefore before the outbreak of plague (which occurred in 1894), with an idiopathic glandular enlargement occurring in children in an epidemic form. The enlargement, he states, involved usually only one gland in the neck over the sternomastoid muscle, but at its anterior border. Apparently, therefore, the adenitis affected the superficial and not the deep cervical lymphatics, which are those usually affected in glandular fever. He mentions the occurrence of these cases in the course of a discussion of *pestis minor*, without, however, suggesting that they were examples of mild plague. It must be admitted that glandular fever does in the nature of its local lesion present a certain resemblance to the mildest form of bubonic plague (*pestis minor*). It is a curious fact, taken in conjunction with the extension of bubonic plague in the East since 1894, that it has been recognized in the far East for some years that a disorder characterized by enlargement of the lymphatic glands, usually those in the inguinal region, might occur in epidemic form both on board ship and in regiments ashore. Although it has only recently been described (by Godding), many medical officers, both naval and military, appear to have been acquainted with the disorder under the name 'non-venereal bubo.' The glands usually affected are the inguinal, and Skinner has suggested that as the 'non-venereal bubos' in the cases he observed invariably occurred in the inguinal glands, and as the patients always had irregular action of the bowels, sometimes dysentery, and at other times apparently constipation, the enlargement of the inguinal glands may be due to secondary infection from the mesenteric lymph glands. The analogy between this theory of non-venereal bubo and that advanced by von Starck for glandular fever will be observed."

DIAGNOSIS.—This is to be made from the symptoms, particularly the cervical adenitis; the diseases to be excluded are pharyngitis, tonsillitis, mumps, leukæmia, and (in severe cases) typhoid fever.

PROGNOSIS is good except when the case is complicated by nephritis; in the Ohio epidemic referred to above there were no recurrences or sequelæ, and only one patient died, and she was a delicate child who had just had scarlet fever.

"The beginning of convalescence is in many, perhaps the majority, of the severer cases marked by the passage of thin greenish stools containing much mucus" (Dawson Williams).

TREATMENT is almost entirely symptomatic. Isolation is necessary, in order to prevent the spread of the disease. Rest should be insisted on; and the pain may be relieved by hot or cold applications. Iron, cod-liver oil, light but nutritious food, and general hygienic surroundings are all indicated. Calomel has been recommended, but it has also been condemned. Applications of belladonna are serviceable for the adenitis, and sodium salicylate should be given in the early stage of the disease when the fever is high and the pain severe.

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GONORRHOEA, THE MORE RECENT PATHOLOGY

OF.—The old conception of gonorrhœa as a disease essentially local in character is rapidly being replaced by a recognition of the frequency with which the gonococci enter the circulation and give rise to pathological conditions in regions of the body remote from the seat of primary infection. Few physicians acquainted with the extensive literature on the extragenital localizations of gonococcal infection that has come into existence during the last fifteen years will think of this disease as a genito-urinary condition pure and simple. Gonococcus infections as a result of their ubiquitous pathology are now admitted into the field of internal medicine. With this growth of knowledge concerning the pathological and clinical importance of this disease there has gradually developed also a respect for its position as one of the most serious infectious diseases of the human race. No medical man of to-day possessed of wide reading or much clinical experience will look upon gonorrhœa as a local infection of relatively slight importance. As an agent of human suffering the gonococcus has acquired a status equal to that of the tubercle bacillus. When one considers the innumerable complications and sequelæ and the radical character of the operations so frequently necessary the mortality from this disease appears nearly if not quite as great as that from any other single infectious disease.

1. GENERALIZED GONOCOCCUS INFECTION.—General symptoms due to the gonococcus may occur as the result either of *intoxication* or of a *metastasis* of the gonococci through the blood or lymph.

A. Gonococcal Intoxications.—Opinions differ as to the nature of the poison produced by the gonococcus. Wassermann, Nicolaysen, Laitinen, Cantani, Gross and Kraus, Jundell, Finger, Ghon, and others believe in an endotoxin, inasmuch as filtered cultures when injected produce no reaction; while on the other hand sterilized cultures do cause one. According to Wassermann 0.1 c.c. of gonococcus toxin injected into man will cause within four hours slight chill, malaise, pains in the head, extremities, and joints, and a local inflammation. The general symptoms last for about twenty-four hours, but the seat of the injection remains inflamed for several days. Repeated injections have no immunizing effect. As the result of his experimental studies Wassermann believes that during the course of a gonorrhœal infection the dead and disintegrating gonococci contained within the body liberate the gonococcal toxin and that marked symptoms of intoxication may result. The degree of intoxication will depend, of course, upon the seat of the infection and the conditions under which it occurs. Upon a mucous membrane the toxin may be washed away before symptoms of poisoning are produced, while in the case of internal localizations of the infection, or when the disease is found in the deeper glands of the genito-urinary tract, severe general symptoms may develop.

Gross and Kraus, Nicolaysen, Laitinen, Finger, Cantani, and Jundell have confirmed Wassermann's findings; the experiments of Steinschneider alone have been contradictory. On the other hand, de Christmas claims that there is contained in filtered cultures of the gonococcus a non-dialyzable body, destroyed at temperatures higher than 75°, soluble in glycerin and precipi-

table by ammonium sulphide. When injected into the brains of experimental animals death ensues rapidly after the development of a characteristic intoxication. Injection of the toxin into the subcutaneous tissue of animals causes the formation of an antitoxic substance in the blood.

Inasmuch as the nature of the gonococcus toxin is not definitely known, its exact rôle in the development of the disease cannot yet be determined. At any rate the above-mentioned experimental work is sufficient to show that the entrance of the gonococcus into the bloodstream and the liberation of its toxins there can cause a more or less severe general intoxication and possibly also trophic disturbances in various organs. Authorities differ as to which of the conditions associated with gonorrhœa are due to the toxins and which to the local occurrence of the cocci themselves. Balzer holds that gonococcal endo-, myo-, and pericarditis, arthritis, pleuritis, periostitis, and phlebitis are due to the presence of the gonococcus, while the majority of the other complications of gonorrhœa are the result of the toxin.

The general symptoms of gonococcal infection are in many cases similar to those of a light malarial or typhoidal infection, viz., a continuous, intermittent, or remittent fever, malaise, weakness, melancholia, etc. The spleen is often moderately enlarged. Authorities differ as to the frequency of these symptoms in uncomplicated cases of gonorrhœa. Trekaki found moderate elevation of temperature in sixty per cent. of fifty cases of uncomplicated acute gonorrhœa, while other writers find it of less frequent occurrence. The psychological factor is, of course, to be taken into consideration, the general symptoms, or at least the recognition of these, in many cases depending to a large degree upon the patient's mental attitude toward his infection. The intermittent or remittent type of gonorrhœal fever is explained by some writers as due to the fact that the gonococci are easily killed by high temperatures, but increase during the fall of the fever. Cases have been observed, however, of prolonged high fever in which no inhibiting influence upon the growth of the gonococci or upon the virulence of the condition was shown.

B. Metastasis of Gonococci.—The old view that the gonococcus is a pure parasite of mucous membranes must now be abandoned. Numerous cases of gonococcus metastasis have been published in recent years, the identity of the organism in question having been fully established by means of microscopical demonstration in the blood, pus, or sections of tissues, by cultivation, and in a few cases by inoculation of the human urethra. The constantly accumulating evidence leads us to suspect that the entrance of gonococci into the blood is a not infrequent event during the course of an attack of gonorrhœa. Possibly the gonococci enter the blood or lymph in the majority of cases, if not in all; but only in a certain proportion, how great we cannot say at the present time, does such an entrance give rise to general or localized metastatic infections. What the conditions are upon which gonococcus general infections and metastases depend we do not yet know. As a rule they occur in severe cases of posterior urethritis or in marasmic individuals suffering from severe constitutional affections. In some cases they probably play the part of terminal infections. Finger believes that gonorrhœal prostatitis offers an especial opportunity for metastasis, since the blood-vessels of this organ lie so near to the epithelium. Improper or over-zealous treatment of the local infection, individual predisposition, greater virulence of certain strains of gonococci, diminished alkalinity of the blood, etc., are among the various explanations given, but no well-established evidence exists in favor of any one of these views.

The *metastasis* of gonococci may be either *hæmatogenous* or *lymphogenous*. The entrance of the cocci into the blood stream has been demonstrated by Wertheim, Thayer and Blumer, Doleris, Colombini, and other ob-

servers. Cole has collected twenty-nine cases of gonococcus *septicæmia* in which definite proof of the presence of the gonococcus in the blood was made during life. Twelve of these patients died, sixteen recovered, and in one case the result was not stated. The clinical picture was that of a septicæmia or pyæmia. In eleven cases endocarditis was present, the general picture being that of a malignant endocarditis. Six cases were pyæmic in character. In ten of the cases the affection ran a comparatively mild course without metastatic local infections. Such cases may closely resemble typhoid fever in their general symptomatology, and undoubtedly some of them have been regarded as the latter disease. Two of the twenty-nine cases were puerperal. Although only two cases of this kind have been reported, some writers state that twenty-five per cent. of all cases of puerperal fever are due to the gonococcus.

The prognosis in gonococcal septicæmia is grave, especially when endocarditis is present; but the demonstration of the presence of gonococci in the blood does not necessarily mean a fatal issue. Over half of the reported cases recovered, and it is very probable that many of the lighter cases recover spontaneously without any suspicion being aroused as to the gonococcal nature of the condition. On the other hand no one can tell how many cases of septicæmia, pyæmia, and so-called malignant endocarditis of unknown origin are in reality cases of gonococcus infection. The treatment of gonococcus septicæmia is essentially that of septicæmia due to other pyogenic organisms. The vaccine treatment has not yet been successfully applied to this form of septicæmia.

The entrance of gonococci into the neighboring lymph-vessels is a common, if not constant, occurrence in all localized gonorrhœal infections. What part this plays in the extension of the disease is not yet known. Nobl has shown that the local lymphangitis frequently associated with gonorrhœa is due to the presence of the gonococci in the lymphatics. Other observers have demonstrated the presence of the cocci in the lymphatics of the pelvis, and it is not improbable that they may pass into the thoracic duct and thence into the blood stream. Such a chain of events remains, however, to be demonstrated. Nobl, Balzer, and others regard lymphogenous metastasis as playing but a slight rôle in the productions of distant metastases, and regard it as of importance only in the involvement of neighboring glands. Future investigations may completely reverse this opinion.

ENDOCARDITIS.—Although the possibility of an association of gonorrhœa with cardiac disease was pointed out over a hundred years ago, it was not until about the middle of the last decade of the last century that the positive proof of the existence of gonococcal endocarditis was furnished through the demonstration of the organism in pure culture in cardiac vegetations. Over fifty cases have been reported since 1895. From the analysis of the cases collected by Hofmann (1903) and Kulbs (1905) it is now possible to make some definite statements concerning the pathology and clinical characteristics of this form of gonococcus localization.

Young males are more frequently affected, but cases have been observed in young children and in old individuals. It appears in two clinical forms, either as a simple endocarditis or as a malignant form. The *simple* form is probably not rare. How frequent it is we cannot say at the present time, but future clinical observations will probably show that it is much more common than is now suspected. It occurs usually during the early stages of an attack of gonorrhœal urethritis, and runs a mild and short course. It may be discovered only by accident, since the general symptoms may be very slight. Fever may be wholly absent. The only sign of a cardiac involvement may be a blowing murmur in the mitral area with a moderate or slight hypertrophy of the left heart. More rarely the aortic valve is affected. The termination may be that of apparent healing, or a valvular lesion of slight degree may be left.

The *malignant* form of gonococcus endocarditis runs a course similar to the malignant affections of the heart valves caused by the other pyogenic organisms. It occurs later in the course of a gonorrhœa, and usually in association with arthritis, but in some cases it appears as the only complication of the local process. Its course is marked by chills, a continuous intermittent or remittent fever with evening exacerbations, and severe subjective symptoms. The general picture is that of pyæmia or septicæmia, but certain symptoms such as dyspnoea, pain in the precordium, etc., direct attention to the heart, where the presence of a murmur and the physical signs of an hypertrophy complete the diagnosis. The disease runs a very malignant course, and only rarely does it terminate in healing. In the latter case there is always a persisting valvular lesion. The aortic flaps are most frequently affected, but there is a striking tendency toward the involvement of the valves of the right side. Embolism and the formation of embolic infarcts occur infrequently, but have been reported as complications of the gonococcus form of endocarditis.

At autopsy there is usually found upon the affected valve a grayish or yellowish-red polypoid thrombus mass. Ulceration and perforation of the flaps are common events; and the ulcerative process may extend deeply into the myocardium. The presence in the vegetations of the gonococci may be demonstrated by staining or by cultivation, although the latter method may yield negative results. In some cases there is a secondary infection with streptococci or staphylococci. Several writers have noted the fact that the gonococcus infection seems to have a predilection for valves already diseased. Of the pathology of the simple form of gonococcal endocarditis we as yet know nothing. It is possible that these mild infections play a part in the development of many of the forms of chronic endocarditis of unknown etiology.

The diagnosis of gonococcal endocarditis during life may be made by means of blood cultures. A special medium is not necessary. Ten cubic centimetres of blood obtained from a large vein under proper precautions may be poured in a thin layer over an agar plate and allowed to clot. The colonies develop at body temperature within one to two days. Aside from this absolute method of diagnosis the occurrence of a cardiac lesion in an individual who has recently had a gonorrhœal urethritis makes the diagnosis of a localization of the infection upon the endocardium very probable. In the light of our present knowledge the systematic examination of the heart in all cases of gonorrhœa becomes advisable.

The treatment is similar to that of other forms of endocarditis. Rest, the precordial ice bag, etc., are the methods usually employed during the acute stage.

The prognosis in the mild forms is good; in the malignant, very grave.

MYOCARDITIS.—Gonococcus myocarditis may occur as an extension of an ulcerative valvular process, but it is rare as an independent affection. Councilman has described a case in which ten days after the beginning of the urethritis an arthritis developed, followed by dyspnoea and pain in the precordium. There was no fever. Death occurred five weeks later. At the autopsy a hemorrhagic pericarditis was found with areas of hemorrhagic necrosis throughout the myocardium. Gonococci were demonstrated in the smears made from the pericardial fluid and the necrotic areas. Iwanoff saw a case of gonococcus abscess in the wall of the left ventricle.

PERICARDITIS.—This affection appears to be a not infrequent complication of gonorrhœa, but rarely occurs as an independent gonococcal localization. It is usually associated with endocarditis and myocarditis. It may occur without symptoms, or may run a comparatively light course. The termination is usually favorable. Both a dry and an exudative form occur. The exudate may be serous or hemorrhagic. The pathology is not different from that of the ordinary forms of peri-

carditis, and the usual physical signs accompany the two varieties. The gonococcal nature of the process can be determined only through the demonstration of the gonococci in the exudate.

PLEURITIS.—This condition is also regarded by a number of writers as a not infrequent complication of gonorrhœa, but the proof of the etiological rôle of the gonococcus has not been furnished in the majority of the cases. Only in a few instances have the gonococci been demonstrated in the fluid obtained by aspiration. Judging from the reported cases, gonococcus pleuritis is usually unilateral, but may be bilateral. It may be of the dry or the exudative variety. In the latter case the amount of exudate is usually small. Other serous membranes are usually coincidentally affected. The prognosis is relatively favorable.

PNEUMONIA.—Both lobar and lobular pneumonia have been observed to occur during the course of gonorrhœal arthritis, but that these were gonococcal infections of the lungs has not been proved beyond all doubt, although in a certain number of cases it is very probable that they were actually due to the gonococcus. Jicinsky, Scholz, Bressel, and others have observed organisms which they regarded as gonococci in the sputum of pneumonic patients suffering from generalized gonococcus infections. In Bressel's case the gonococci were also cultivated from the blood. Too little is known of the pathology and clinical character of such pulmonary localizations of the gonococcus to make any definite statements concerning them.

PERITONITIS.—It was formerly held that the peritoneum was immune to the gonococcus, but the frequent occurrence of a localized gonococcal peritonitis was demonstrated in 1891 by Wertheim, and the almost constant association of such local inflammations of the peritoneum with gonorrhœal salpingitis was soon recognized by gynecologists. Pelvic peritonitis in the male as a complication of prostatitis, cystitis, and vesiculitis was later recognized as another pathological and clinical possibility. According to the reported cases the chief symptom of such a complication is the occurrence of intense pain in the inguino-scrotal region. The duration of the condition is usually short and the prognosis is favorable. In more recent years the existence of a pure generalized gonococcal peritonitis has been repeatedly demonstrated. These cases occur chiefly in young girls and women as a complication of salpingitis. The symptoms are similar to those of general peritonitis caused by the pyogenic cocci, although, as a rule, the gonococcal infection runs a milder course. The prognosis is more favorable in the latter condition. The differential diagnosis is difficult and rests chiefly upon the coincidence of a gonorrhœal salpingitis.

APPENDICITIS.—In a large number of cases of gonorrhœal salpingitis the appendix shows likewise the presence of a purulent inflammation of a relatively mild type, although the suppurative form may also occur under such conditions. To what extent this coincidence is accidental, or what per cent. of these cases is due to secondary or associated pyogenic infection, or actually to the gonococcus cannot be stated at the present time. Although gonococci are said to have been found in the inflamed appendix, the bacteriological proof is not yet fully established.

INTESTINE.—Gonorrhœal proctitis as a primary or secondary condition is common enough and has long been recognized. *Perirectal abscesses* may also be caused by gonococci, even when there is no involvement of the rectal mucosa. More recently metastatic gonococcal lesions in the colon have been observed. The entrance of gonococci into the lymphatic vessels of the pelvis has also been demonstrated and their passage into the thoracic duct and thence into the blood becomes a possibility the demonstration of which remains for future investigators.

LYMPHANGITIS.—A proliferative exudative endolymphangitis, usually associated with a perilymphangitis, has recently been discovered to be gonococcal in origin.

The lumen of the lymphatic is gradually obliterated by the fibroblastic proliferation of its walls, and the vessel becomes converted into a greatly thickened cord-like structure. Areas of an infiltration with mononuclear cells are found in and near the vessel walls, and the gonococci may be demonstrated in the vessel as well as in the neighboring tissues. The lymphatics most frequently affected are those of the pelvis and genitalia. Chronic œdema and elephantoid thickenings may develop in the region tributary to the obliterated lymph vessels.

PHLEBITIS.—Heller in 1904 collected twenty-six cases of phlebitis occurring in association with gonorrhœa. The part played by the gonococcus in these cases of phlebitis is not yet known with certainty, although it seems very probable that the gonococcus itself may be the direct cause of the venous affection in some cases, while in others the condition may be due to a secondary infection with one of the pyogenic cocci. The veins of the lower extremity are usually involved; and the clinical picture is the same as that of other forms of infectious phlebitis, and the treatment is identical.

ARTHRITIS DEFORMANS.—Recent writers have suggested that gonococcal infections may be the cause of a certain per cent. of the cases of arthritis deformans. The fact that permanent changes in the joints frequently follow severe or repeated attacks of gonorrhœal arthritis has suggested a close relationship between the latter condition and arthritis deformans. Stewart found a history of gonorrhœal infection in thirty per cent. of his cases of arthritis deformans. Other writers, however, have found such a history in a much less per cent. of their cases. Further evidence in favor of the view may be found in the fact that a number of cases of *spondylitis deformans* following repeated attacks of gonorrhœal arthritis has been reported. The evidence is as yet insufficient, and the question of the relationship between gonococcal infection and arthritis deformans must be left to future investigations for its settlement.

PAINFUL HEEL.—Recent studies of this affection have made it certain that in the majority of cases it is gonococcal in origin. The condition usually develops in association with or after an attack of urethritis, and is often seen in connection with arthritis. Gonococci have been demonstrated locally in pure culture. The most striking pathological finding is a new formation of bone on the plantar surface of the heel, usually at the point of origin of the *M. flexor brevis digitorum*. The early changes preceding the formation of the exostosis are not yet known, but are probably of the nature of a local periostitis. Removal of the bony growth relieves the symptoms.

GNOCOCAL PERIOSTITIS, OSTEOMYELITIS, PERICHONDRITIS, CHONDRITIS, TENOSYNOVITIS, MYOSITIS, ADENITIS, and MASTITIS have all been positively demonstrated by the finding in the pus or the exudate of gonococci in pure cultures. The number of such cases is at the present time very small, and the frequency of such metastases is not known. Likewise but little is known of their pathology and symptomatology. They may occur independently or in association with other localizations of the infection.

KIDNEY.—Gonococcal lesions of the kidney exist in two forms, an ascending pyelonephritis and metastatic abscess. The writer has seen a case of gonococcal *perinephritic abscess*, demanding radical operation, develop in a young man during the course of an acute urethritis. Gonococci were found in the pus. Numerous cases of *pyelitis*, *pyonephrosis*, and *ascending pyelonephritis* have been reported as occurring during the acute stage of gonorrhœa, but in few of these has it been possible to demonstrate positively the gonococcal origin of the process.

NERVOUS SYSTEM.—Gonococcal meningitis has been reported. The gonococci were obtained from the exudate. The association with gonorrhœa of symptoms pointing to an involvement of the brain or cord has

long been recognized, but the nature of this association has not yet been determined. *Myelitis, meningomyelitis, polyneuritis, neuritis*, etc., occurring with or after an attack of gonorrhœa, have been regarded as the result of the infection, but no direct etiological relationship has been definitely shown for some of these conditions. Some of the gonorrhœal neuralgias, the sciatica often seen in connection with the disease, and the local neuritis associated with gonorrhœal arthritis, appear to have a definite relation to the infection, probably through secondary involvement or as the result of the action of the toxin. As is well known, there frequently occur in chronic gonorrhœal infections, particularly in chronic prostatitis, well-marked *psychoneuroses* of great clinical importance. Some of these conditions are probably purely psychical and have nothing to do either with a localized action of the gonococci or their toxins.

EYE.—Metastatic *tenonitis, conjunctivitis, keratitis, iritis, iridocyclitis, iridochoroiditis, retinitis, neuroretinitis, optic neuritis*, and *dacryo-adenitis* have been reported as associated with gonorrhœa. The exact relationship of these conditions to the gonococcal infection has not yet been demonstrated. Whether they are the result of a localization of the gonococci or the effect of the gonococcus toxin remains to be shown in so far as the majority of these affections are concerned. In the case of the conjunctivitis the presence of gonococci has been demonstrated, and the special features of the condition make it very probable that it is actually metastatic in origin. Both eyes are affected and it runs a much milder course than the direct infection, although showing a tendency to recurrence. Iritis and arthritis are usually associated with it. The occurrence of *iritis* in association with gonorrhœal arthritis may also be mentioned as one of the relatively rare complications of gonorrhœa. While regarded by some writers as metastatic in origin, no absolute proof of this has yet been offered.

SKIN.—Various forms of skin eruptions have been noted as occurring in association with gonococcal infections. *Erythema simplex and nodosum, urticaria, hemorrhagic and bullous eruptions, hyperkeratosis*, etc., have been frequently observed in cases of gonococcal septicæmia. Gonococci have been demonstrated in some of these skin lesions, but in the majority positive proof of the etiological relationship is wanting. Some writers regard the skin lesions, particularly the hyperkeratosis, as trophic in character, the result of the action of the toxins upon the nerve endings.

Besides the numerous metastatic localizations of gonococcal infection discovered in recent years, various forms of direct primary or secondary infection not previously recognized have been recorded.

GNOCOCAL STOMATITIS.—In 1898 Jesionek demonstrated by cultivation the presence of gonococci in round, slightly elevated, grayish-white lesions of the mucous membrane of the mouth cavity. As a rule these lesions do not ulcerate, although the largest ones may show slight erosion. The tongue and mucous membranes are usually red, tender, and swollen. Vesicles containing gonococci may develop upon the lips. The sublingual glands may become involved. The affection may be found in adults, but is most common in young infants as the result of infection received during birth.

GNOCOCAL RHINITIS and PHARYNGITIS have also been reported, but without satisfactory proof of the presence of gonococci.

GNOCOCAL MASTITIS has been observed as a direct infection. The writer has seen a case in which amputation of both breasts was performed as the result of a virulent gonococcal suppurative process, the infection apparently having been transferred by the nursing of an infant whose eyes and mouth were the seat of a gonococcal inflammation.

Gonococcal infection of the *umbilical cord* has been seen by a number of writers. The occurrence of a purulent inflammation of the placenta due to gonorrhœa has also been recorded.

Wound infections due to gonococci have been reported by Juilliot, Meyer, Young, Cole, and others. Infection of the wound following operations for gonococcal arthritis, inguinal hernia, etc., have been reported, as well as gonococcal infections of finger wounds.

The occurrence of *epidemic gonorrhœal vaginitis* in children's hospitals has recently attracted a good deal of attention. The affection is nearly constantly present in the infants' wards of large city hospitals, and from time to time becomes epidemic. The conditions obtaining in such wards favor the spread of the infection, and it must also be assumed that the vulvovaginal mucosa of infants is very susceptible to the infection. Many cases apparently run a mild course, but the affection resists treatment, and after reaching a chronic stage may be accompanied by any of the complications attending gonorrhœa in the adult female. Salpingitis, peritonitis, and arthritis are the most common of these secondary localizations. Sterility or chronic valvular lesion may be the sequelæ of such infantile infections. The after-history of such cases has not been followed out to any extent. In a case of infantile gonorrhœa with arthritis seen by the writer, all four of the heart valves showed minute vegetations. Some writers call attention to the suspicion of gonococcal infection attending all cases of peritonitis and arthritis in girl babies.

In the case of gonococcal arthritis occurring in infants without other apparent localization of the infection it is possible, as Holt has suggested, that the mouth forms the portal of infection. Particularly in the case of male babies does such a supposition at times seem justified.

OPSONIC INDEX IN GNOCOCAL INFECTIONS.—The investigations carried out by Cole and Meakins concerning the opsonic index to the gonococcus in cases of gonorrhœal arthritis showed that in twenty-five cases of gonococcal infection a low index was present before the use of vaccines. In fourteen cases of non-gonorrhœal infection a higher index was found. Inasmuch as a low index would be found in those cases in which an acute urethritis is present the determination of such an index would not throw any light upon the nature of a coincident metastatic infection. In cases of suspected gonococcal arthritis or other localization a high or normal index may be taken as evidence against the gonococcal nature of the infection. As Cole points out, the accuracy and value of this method of diagnosis are not yet determined. That any conclusions be drawn at all it is necessary that the variation in the index exceed the possible variation in technique.

RECENT METHODS OF TREATMENT.—Cole and Meakins report results, regarded by them as encouraging, in the treatment of gonorrhœal arthritis by vaccines prepared by heating an emulsion of gonococci in 0.85-per-cent. salt solution for one hour at 65° C. The number of the cocci per cubic centimetre is estimated by an especial method, and an initial dose of 200 million cocci is given, and this dose is repeated or increased as the index is falling. Doses of 500–1,000 million cocci may be given every seven to ten days. While the number of cases so treated is too small to give us any well-founded ground for believing the method to be of great value, the results show that no apparent harm is done and that there was an unusual degree of improvement following the use of the vaccines. Whether such an improvement is actually due to the vaccines must be shown by the study of a large number of cases so treated. The best results were obtained in the chronic cases, and it is in just such cases that the psychical factor plays such an important rôle. The authors mentioned do not regard the opsonic index as a necessary guide in the control of the treatment, and express their disbelief in the danger of cumulative negative phases.

The use of an *antigonococcus serum* has been advocated by Rogers, Torrey, and others, but up to the present time no convincing results have been obtained by the experimental investigations bearing upon the em-

ployment of such sera in the treatment of gonorrhœal conditions.

Aldred Scott Warthin.

GUAIASANOL (Guajasanol) is chemically the hydrochloride of diethylglycocol-guaiaicol, having the formula $C_{15}H_{19}NO_5HCl$. It crystallizes in white prisms, has a melting point of $184^{\circ}C$, with a faint odor of guaiaicol; is easily soluble in water, aqueous solutions being neutral. The addition of alkaline carbonates to aqueous solutions of guaiasanol liberates the basic diethylglycocol-guaiaicol, which has the appearance of oil.

Pharmacological experiments show this preparation to be antiseptic, deodorant, and anæsthetic, non-poisonous even in large doses, subcutaneous injections of 45 grains in rabbits not being followed by toxic symptoms.

The indications for use of guaiasanol are the same as for that of creosote or guaiaicol. It is well borne in phthisis, being followed by improvement in appetite. In tuberculous ulcerations of the throat it can be used locally, by mouth, or subcutaneously. It is also useful as an intestinal disinfectant in diarrhœa, tuberculous diarrhœa being often controlled after the administration of a few doses. In purulent cystitis and as a disinfectant in bladder troubles it is used in irrigations, $\frac{1}{4}$ to 3 parts in 1,000, or administered by the mouth in doses of 120 grains per day. It has a favorable effect on septic diseases; is recommended as a deodorant in ozœna in tampons saturated in a ten-per-cent. solution and changed every half-hour. In ulcerations of the bones, eruptions, sarcoma, purulent carcinoma, etc., it is applied in two-per-cent. solutions in compresses; in malodorous stomatitis as irrigations one-half to two-per-cent. or five-per-cent. solutions for painting; in ophthalmology, for all superficial wounds of the eye in one-per-cent. solutions, there being when thus used quite a perceptible anæsthetic effect. Finally it is used in chronic inflammatory conditions of the connective tissue, where an astringent or corrosive agent is not tolerated, in one-per-cent. solutions.

Dose of guaiasanol internally is from 45 to 180 grains per day, or subcutaneously 45 to 60 grains in concentrated aqueous solutions.

John W. Wainwright.

HÆMOLYSIS.—(Synonyms: Hæmocytolysis; Hæmatolysis; Laking of blood; Globulysis; Erythrocytolysis.)

Although etymologically this term includes destruction or solution of both red and white corpuscles, yet by usage it has come to be applied, when used without specification, only to the erythrocytes. When corresponding changes of the leucocytes are considered, the specific term *leucolysis* or *leucocytolysis* is generally used. In this article the term hæmolytic will be used, as above indicated, to apply only to *erythrolytic*.

In hæmolytic the essential phenomenon consists in the escape of the hæmoglobin from the stroma of the corpuscles into the surrounding fluid. As it is not exactly known in what way the stroma holds the hæmoglobin normally, whether purely physically or in part chemically, or whether the stroma consists of a spongioplasm or a sac-like membrane, or both, the ultimate processes that permit the escape of the hæmoglobin are not finally solved. However, the agents by which the escape is brought about are well known and extensively studied, and they are found to be of extremely various natures. They may be roughly classified as: (1) Known physical and chemical agents; (2) unknown constituents of blood serum; (3) bacterial products; (4) certain vegetable poisons; (5) snake venoms.

While the known chemical and physical agencies in the production of hæmolytic have much significance in physiology, and to some extent in pathology, yet the importance of the subject of hæmolytic at the time of this writing rests chiefly upon the work now being done with blood serums; and in turn the chief importance of this work lies in its relation to problems of bacterial destruction, cell destruction, and the general laws of cell susceptibility and cell resistance. Hence we shall devote particular attention to the subject of serum hæmolytic,

appreciating that whether time does or does not show this work to be of as far-reaching importance as is now hoped, yet in any event it will mark a distinct period in the history of medical science. As being by far the simpler, however, we shall first discuss:

(1) HÆMOLYSIS BY KNOWN CHEMICAL AND PHYSICAL AGENCIES.

If distilled water is added to corpuscles of any kind, osmotic changes are bound to occur, since within the cells are abundant salts, soluble in water, which will begin to diffuse outward in an attempt to establish osmotic equilibrium between the corpuscles and the surrounding fluid. Conversely water enters the corpuscles at the same time, and accumulating there leads to swelling until such injury has been produced as permits the hæmoglobin to escape and enter the surrounding fluid. Before this occurred the fluid was opaque because of the obstruction to light offered by the red cells. The stroma now settles to the bottom, while the hæmoglobin diffuses into the fluid, making it red, but perfectly transparent. This process has long been known as the "laking" of blood, and is essentially the condition present in all forms of hæmolytic. That the hæmoglobin escapes only through injury of the stroma and not through simple osmotic diffusion is shown by the fact that if salt solution of the same concentration as normal serum is used instead of distilled water, no such escape of hæmoglobin occurs. As hæmoglobin is perfectly soluble in the salt solution it should pass out if it diffused as do the salts. Since there is no escape of hæmoglobin in such a salt solution, it is evident either that the stroma is not permeable to hæmoglobin, or else the hæmoglobin is in some way attached to or combined with the stroma. Again, if the corpuscles are placed in a solution of salt more concentrated than their own fluids, water escapes and the corpuscles shrink; as no hæmoglobin escapes with the water it is evident that the stroma is not permeable to hæmoglobin when intact. Therefore it would seem that hæmolytic by distilled water may be purely physical, produced by the cell stretching until rupture occurs and the hæmoglobin escapes as from a sac, or else it may be that the stroma is partly soluble in water but not in salt solution, so that the distilled water dissolves the stroma and the hæmoglobin escapes from its attachment. Because of the resemblance of the process of hæmolytic to the rupture of plant cells with escape of their contents when they are placed in distilled water, it might be assumed that hæmolytic is largely a physical matter, but there are many indications that chemical changes must be involved. For example, if a red corpuscle in an isotonic solution is cut into pieces the hæmoglobin does not escape, indicating that its structure is quite dissimilar to that of the simple vegetable cell, and that there is some union of stroma and of hæmoglobin other than physical.

Repeated alternate freezing and thawing is another physical means of bringing on hæmolytic. Heating to 62° – $64^{\circ}C$ causes hæmolytic of mammalian corpuscles; in cold-blooded animals this seems to occur at a slightly lower temperature.

Some chemical agents, as might be expected, are capable of liberating hæmoglobin, even when the corpuscles are in isotonic solutions. The ordinary salts of serum, of course, do not have this property, but ammonium salts are strongly hæmolytic. Urea also will dissolve red corpuscles. The chemical agents that dissolve red corpuscles seem to be those that have the power of penetrating the stroma. Ammonium salts and urea penetrate the corpuscles freely and cause hæmolytic. Sugar and NaCl seem not to penetrate the corpuscle, and therefore do not produce hæmolytic. Of the permeating substances there seem to be two types: One, like urea, does not produce hæmolytic when in a solution of NaCl isotonic with the serum; the other, like ammonium chloride, is not prevented from producing hæmolytic by the presence of NaCl. All these agents seem to effect hæmolytic by acting on the stroma, for when the stroma of corpuscles

hardened in formalin has its lecithin and cholesterin removed with ether, saponin, a powerful hæmolytic substance, seems to have no effect. The action of saponin and of many other hæmolytic agents can be prevented by the presence of cholesterin in excess, suggesting that it is this constituent of the stroma that is affected. The fact that chloroform, ether, and amyl alcohol will cause laking is probably intimately connected with the fact that lecithin and cholesterin, important constituents of the stroma, are both soluble in these substances. Arseniuretted hydrogen when inhaled causes intravascular hæmolysis, and there are many other drugs and chemicals with the same property, among which may be mentioned nitrobenzol, nitroglycerin, and the nitrites, guaiacol, pyrogallol, acetanilid, and numerous aniline compounds. The bile acids and their salts will also produce hæmolysis, as seen in jaundice. Sodium bicarbonate solutions of one or two per cent. are hæmolytic for some varieties of corpuscles, but 0.1 per cent. Na_2CO_3 and NaHCO_3 do not cause hæmolysis.

Leucocytes are dissolved by some of these agents, particularly the bile salts, although they are affected by no means so rapidly or so much as are the erythrocytes. There seems to be no relation between the erythrolytic and leucolytic powers of these substances. Water causes swelling, with solution of the granules in time, and the same is true of ammonium-chloride solutions.

(2) HÆMOLYSIS BY SERUMS.

With these facts as to the physical and chemical properties of the red corpuscles, we may consider the features of serum hæmolysis. Since a very early time it has been known that it is not possible to substitute the blood of animals for the blood of man by transfusion, because the corpuscles of both transfused and native blood soon suffer destruction. Animal experiments also showed that as a general rule the blood of one animal cannot be substituted for that of another of a different species. This observation was not extended, however, until attention was drawn to it later by experimental investigations that may be said to have begun with the observations of Belfanti and Carbone. They found that if the red corpuscles of a rabbit were injected into a horse repeatedly, the serum of the horse became very toxic for rabbits, because it caused dissolution of their red corpuscles. It also developed that this same hæmolytic property was manifested when the serum was added to rabbit corpuscles in a test tube. When Bordet showed the similarity of this process with the solution of bacteria by serum, a process that had already been studied in a similar manner, the phenomenon of hæmolysis by serum suddenly leaped into importance, and has now for some time occupied the attention of a large part of the bacteriologic and pathologic laboratories of the world. In hæmolytic experiments we have a means of studying the property of blood serum of destroying cells under varying conditions, which is extremely easy to observe and control as compared with the less readily examined bacteria or tissue cells. Whatever the future may develop as to their ultimate worth, there can be no doubt that hæmolysis experiments have given us many new and clear conceptions of the means of defence of the body against bacteria, and also of changes in cells of other sorts, that would not have been secured by any other method.

The manner of conducting hæmolysis experiments is usually about as follows: Blood corpuscles of the kind to be tested are secured by defibrinating the freshly drawn blood in the usual way, by whipping. A five-per-cent. solution of these corpuscles is made by adding 19 parts of 0.75 per-cent. NaCl solution, which is isotonic with them. This emulsion is placed in test tubes, very small ones by choice in order to save material, and the serum that is to be studied is added to it. It is necessary that the tubes be cleaned as for chemical research and sterilized, and all steps of the experiments should be under aseptic precautions to prevent bacterial action affecting the experiments. As Jordan has shown that even the degree of

alkalinity possessed by some varieties of glassware when new may cause hæmolysis, the tubes should be cleaned with the usual acid cleaning fluid. The tubes, stoppered with cotton, are kept at 37°C ., and in the course of from fifteen minutes to two hours the hæmolysis will be manifested by the diffusion of the hæmoglobin upward into the supernatant fluid, while the turbidity produced by the red corpuscles disappears. At the bottom of the test tube the stroma collects as a slight sediment.

The Mechanism of Hæmolysis.—If a serum from an animal immunized against the red corpuscles of another animal is allowed to act upon such red corpuscles in a test tube, hæmolysis occurs promptly. Bordet showed that this property was lost if the serum was heated half an hour at 55°C ., indicating that the destroying agent was very sensitive to heat. In addition he found that if to such heated serum, deprived of all hæmolytic power, there was added a small amount of serum from an animal that had not been immunized and which was of itself inert, the combination was quite as active as the unheated immune serum. In other words, there is contained in normal serum a substance easily destroyed by heat, that needs to be present to cause such specific hæmolysis. But this *thermolabile* substance alone is not able to dissolve the red corpuscles, as the normal serum is found to be quite inactive; it is necessary also to have present some second substance that appears in the serum during the process of immunization. And as heated serum is also quite inactive it is apparent that this heat-resisting (*thermostable*) substance is not of itself able to dissolve the corpuscles. Therefore evidently two substances are needed to dissolve the corpuscles: one, which is easily destroyed by heat and which is present in normal serum; the other, which is present in sera of immunized animals, and which resists heat. Before Bordet had demonstrated these facts about the red corpuscles he had found out that the same conditions prevailed in the destruction of cholera spirilla by the serum of animals immunized against them—two similarly behaving bodies are required in the solution of the organisms, the so-called "Pfeiffer's reaction." Out of these fundamental observations have grown the vast amount of research on serums in their relation to immunity, and on them have been based the theory of Ehrlich as to the ultimate nature of the processes of bacterial and cellular destruction that protect the body from infection and disease, and which perhaps play a part even in normal metabolism.

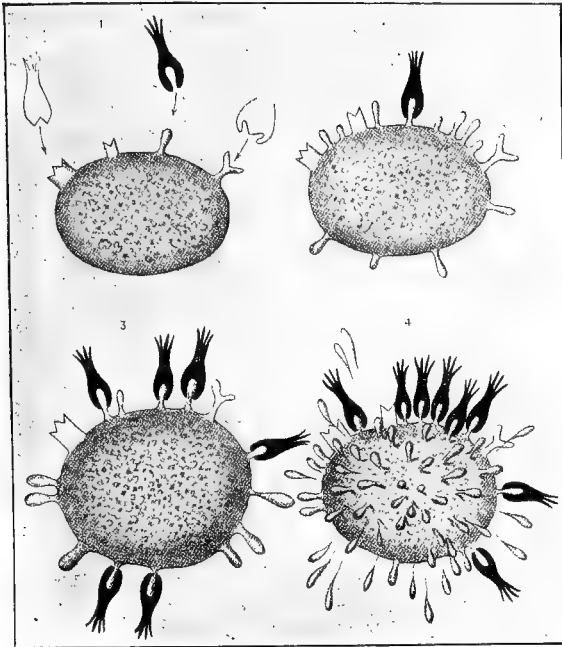
EHRLICH'S THEORY OF HÆMOLYTIC PROCESSES.—Although at this time Ehrlich's ideas stand only as theories, and nothing more, still the fact that they have given us some sort of mental image upon which to base investigations of undoubted value, places them in a certain position of permanence. For this reason we shall endeavor to set them forth briefly in this article.

The Nature of Toxin and Antitoxin.—The fundamental feature of Ehrlich's theory rests upon a conception of the manner in which a toxin attacks a cell. If we consider a cell purely as a mass of various chemicals, and a toxic material as another chemical substance, either simple or complex, it will be apparent that the toxic substance will affect the cell if there is a chemical affinity between them. If there is no such affinity that particular toxic substance is not harmful for that particular cell. On the other hand, if the toxic substance and the cell do possess a chemical affinity they will unite, and the composition of the cell will be altered. When the uniting substance is toxic the result of the union is an injury of some kind to the cell. Undoubtedly other substances may unite with the cell without injuring it, for example, food supplies.

If this line of reasoning be carried still further, it will be readily seen that of the many substances of different chemical nature that compose a cell, not all can have the same degree of affinity for the toxin. By ordinary chemical laws the substance that has the greatest affinity will attract the toxin until it is saturated, and only on condition that there are other substances with affinity of varying degrees will more than the one susceptible substance unite with the toxin. We can thus conceive of

a cell with one or more constituents that may become united to any given toxin with varying readiness. To these cell components that combine with the toxin the name *receptor* has been given by Ehrlich, and is generally applied. It will be readily seen that if a cell is affected

tors for whatever use they may have under normal conditions. Obeying the laws of regeneration the cell replaces these lost groups by new ones; indeed it replaces them in excess, much as in the healing of a wound there



FIGS. 5167 and 5168.—Ehrlich's Diagrams Illustrating the Mechanism of Immunity and Cytotoxicity. 1, 2, and 3 illustrate different forms of receptors, showing the necessity for agreement of the combining bodies. The figures in black indicate substances with toxic action. 4, 5, and 6 illustrate the excessive production of receptors in response to the action of toxins, and their escape from the cell; in 6 they are seen to combine with toxin outside the cell, preventing its union with the cell; 7 shows the structure of the complement and intermediary body of bacterolytic and cytolytic sera; 8 shows the amboceptor, while attached to the cell, uniting the complement to a large molecule.

by a toxin that fact implies the presence in the cell of a receptor for the toxin. Conversely an absence of proper receptors will explain the lack of susceptibility of certain other cells to the same toxin. For example, we may consider that some animals are immune to tetanus because the cells of their nervous systems contain no receptors that will combine with the tetanus toxin. To make the analogy to chemical reactions, Ehrlich has likened the receptors to the various *side chains* of organic compounds.

Figs. 5167 to 5171 represent in diagrammatic form the principles involved, in which definite forms are made to indicate chemical groups, and differences in their configuration to indicate differences in chemical affinity. The protrusions from the cells indicate the receptors or "side chains" that combine with outside substances. Each particular variety of receptor combines with the particular toxin for which it has a chemical affinity, as indicated by correspondence of configuration. In these diagrams toxic bodies are always indicated in black; and the black objects represent toxins which combine with the particular receptors they fit, or, in other words, for which they have a chemical affinity.

The body known as antitoxin is evidently one that has the power of combining with the toxin, for it has been demonstrated repeatedly that mixtures of toxin and antitoxin in proper proportion that have stood together a short time are quite inert; the union seems to be after the nature of the union of chemicals. This fact likens antitoxin to the receptors which have just been described, and in fact it is considered that antitoxin and receptor are identical substances, with the difference that the receptor is a part of a cell, while the antitoxin exists free in the serum. Ehrlich's explanation of the formation of antitoxin is as follows: When the toxin combines with the receptors of a cell, the cell is deprived of these recep-

is an excessive formation of new cells. The excessive receptor bodies fall away from the cell into the serum, where, if they meet with any toxin, they will combine with it just as well as if they were still attached to the cell. Of course if the toxin is saturated with receptors while in the serum, it is devoid of any affinity for the receptors attached to the cells and does not harm the cells. In this way the cells are protected from the toxin. So, when we inject diphtheria antitoxin into the body of a patient, we are merely introducing receptors from the susceptible cells of a horse.

These meet with the molecules of diphtheria toxin while it is still in the blood, and combining with it there prevent it attaching itself to any of the cells of the patient, and so it is rendered incapable of causing harm. The diphtheria antitoxin is not only able to combine with diphtheria toxin which is in the circulation, but if in excess to wrest from the cells toxin which may have already been combined, probably by the law of mass action. This always happens when a case of diphtheria is cured by

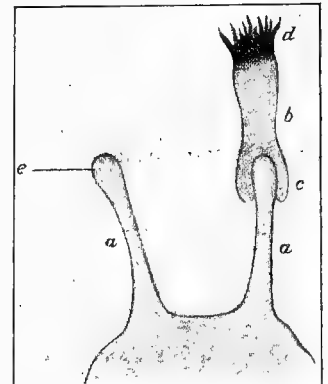


FIG. 5169.—Receptor of the First Order (a). b, Haptophore complex; c, combined toxin molecule, with haptophore (c) and toxophore (d) groups. (After Ehrlich.)

antitoxin, and the clinical evidence of the "wresting" process is the sudden subsidence of the disease. It is not so easy to wrest tetanus toxin from the nervous tissue with antitoxin, and accordingly tetanus is not often cured by antitoxin.

One of the strongest proofs of Ehrlich's conception of antitoxin and toxin is that furnished by Wassermann's experiment.

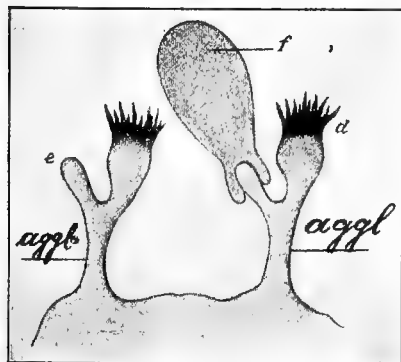


FIG. 5170.—Receptor of the Second Order (aggl), with haptophore (e) and zymophore (d) groups; f, combined food molecule. (After Ehrlich.)

idea that a toxin attacks the cells that have receptors for it, and when so combined is harmless for other cells. In this case the nerve cells have combined with the toxin just as does antitoxin and have rendered it unable to attack other nerve cells. Other tissues are found to be quite unable to fix tetanus toxin in this way. A similar action has been found by Flexner to exist between nervous tissue and the specific nervous poison of cobra venom. The union of toxin and antitoxin seems to be of strictly chemical nature, for it follows the usual laws of chemical union, and it seems impossible to separate again the toxin and antitoxin after they have combined.

No. 4, of Fig. 5167, and No. 5, of Fig. 5168, illustrate the overproduction of receptor groups, which are liberated and enter the blood plasma. No. 6 (Fig. 5168) indicates the combining of the receptors with the toxin molecules, and shows how incapable they now are of combining with the cell.

In the process of immunization, under this conception, the receptors of the cells are repeatedly combined with toxin, and the resulting reaction on the part of the cells causes the discharge of large numbers of free cell receptors into the blood. These receptors give the serum whatever antitoxic property it may have.

The Structure of Toxins.—We have referred to the fundamental conception of a toxic substance as a substance which by combining with the receptor of a cell injures the cell in some way. It has been developed that toxin accomplishes this injury by a portion of itself that is different from the portion that combines with the receptor. In other words, a toxin consists of a substance that binds it to the cell, and of another that causes the injury to the cell. This may be explained best by describing the facts that gave rise to this idea. When a toxin, say tetanus toxin, has been kept for some time, it is found that its toxic action decreases until relatively very large amounts are required to produce symptoms of tetanus in animals. Such a weakened toxin, however, requires just as much antitoxin to neutralize its toxic action as it did while possessed of its full strength. As the antitoxin is merely an accumulation of free receptors, it seems that the toxin during the process of weakening has lost none of its power to unite with receptors, but rather has lost its power to cause injury to the cell. The group that attaches itself to the cell receptor has been called by Ehrlich the *haptophore* group, while the group that injures the cell is called the *toxophore* group. Toxins that have become weakened while still retaining their power to

combine with antitoxin are referred to as *toxoids*, and are supposed to be toxins that have lost the *toxophore* group but have retained the *haptophore* group. In the diagrams of Ehrlich the fringed portion of the toxin figure represents the *toxophore* portion; the part fitting with the receptor, the *haptophore*.

It may be mentioned that this degeneration of toxins into toxoids has practical application in immunization, for since toxoids are just as capable of combining with cell receptors as are toxins, they can be used to produce antitoxin without danger of causing intoxication.

The Relation of Toxins to Hæmolysins.—While the above discussion of the nature of toxin and antitoxin does not directly apply to the subject of hæmolysis, yet it is necessary to an understanding of the principles of cytolytic phenomena, since out of this conception of the nature of immunity against toxin has come our present conception of the nature of immunity against cells. Animals are immunized against foreign blood corpuscles just as they are against bacteria and against toxins, by repeated injections of small amounts of the foreign substance. Similarly in each case their serum comes to contain a substance capable of protecting the animal against the injected material. However, there is one important difference between immunity against toxin and immunity against cells, whether these cells are bacteria, blood or tissue cells matters not. To neutralize a toxin it is merely necessary to occupy the group of the toxin that unites with the cell receptors, for then the toxin cannot unite with the cells to injure them; in this harmless condition the toxin is destroyed or eliminated. In the case of the cells, however, it is necessary that they be destroyed by the serum, and this requires more than the entrance into them of some body from the serum; they must be attacked somewhat in the way a toxin attacks a cell. In fact, a serum immunized against a cell is really a toxin for that cell, and like the bacterial toxins it possesses two groups, one combining with the cell, and the other that attacks the cell. However, there are certain important differences between bacterial toxins and immune serums. It will be remembered that it was found that both bacteriolytic and hæmolytic serums lost the power of producing their specific effects of cell destruction when heated for half an hour at 55° C., and that they regained this power in full when to them was added some normal serum, which alone was quite inactive. From this it was deduced that two substances enter into the cytotoxicity: one susceptible to heat and present

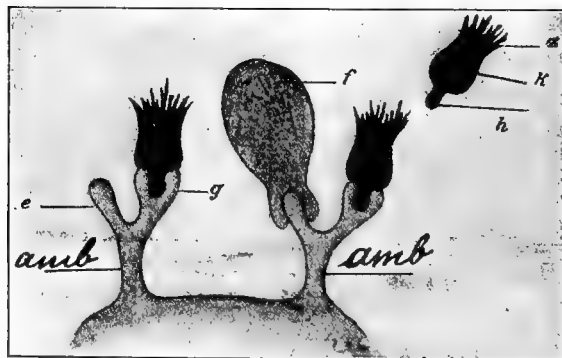


FIG. 5171.—Receptor of the Third Order. amb, The receptor; e, haptophore (cytophile) group; g, complementophile group; K, complement, with haptophore (h) and zymotoxic (z) groups; f, combined food molecule. (After Ehrlich.)

in normal serum, the other more resistant to heat, and present only in immunized animals. Comparing the cytolytic serum with the toxin we see that the chief difference lies in the fact that one of the cytolytic bodies is present normally in the serum, and can be supplied quite readily to make the other body active. In its susceptibility to injurious agents and in its power to

destroy cells this thermolabile substance resembles the toxophore group of the toxin. As it has to be added to the body that is developed during immunization to render the latter active, it has been given the name of *complement*, indicating that it is a complementary substance in the reaction. Another name sometimes applied to the same body, *addiment*, is of similar significance. On the other hand, the body developed in the serum through the process of immunization, is quite like the haptophore group of the toxin, in that it is more resistant to injurious influences, and, as will be shown later, is concerned in uniting the complement to the cell to be attacked. As it has two affinities, one for the cell, the other for the complement, it has been called by Ehrlich *amboceptor*, implying the double affinity. A receptor, for example, having but one affinity may be called a *uniceptor*. Another name commonly given to the amboceptor is *immune body*, because it is the specific substance that confers immunity; but, as this or a similar body may be naturally present in the serum of animals that have not been immunized, this name can be used only for specifically immunized animal serum, and the more general term, *intermediary body*, is used except in specific instances.

The Mechanism of Hæmolysis.—Our understanding of the phenomena of serum hæmolysis is therefore as follows: During immunization the immune bodies are developed, which have the property of combining with the red cells, attaching themselves to the receptors of the corpuscles. They combine on the other side with the complement that is present normally in the serum, even before immunization, and by so attaching it to the corpuscles enable it to exert its destructive action. This arrangement is indicated by No. 7 (Fig. 5168), in which the black fringed body represents the complement, united by the amboceptor to the red cell receptor. Beside it are shown free the two constituents of the hæmolysin. Without being attached in this way the complement is quite inert. That the immune body is attached to the corpuscles is shown by the following experiment: If an immune serum is heated the complement is destroyed, and we have the immune body in an inactive condition in the serum. This inactive serum is mixed with red corpuscles, and kept for fifteen minutes at 45° C.; the red corpuscles are then separated by centrifugalization. The supernatant fluid is removed and added to other red cells. If it still contains intermediary body it should be able to dissolve the corpuscles when fresh normal serum, containing complement, is added. As no hæmolysis does occur it appears that all the intermediary body has been taken out of the serum by the red corpuscles. That this is the case can be proved by adding to these corpuscles some normal serum which contains complement, but no intermediary body, for the corpuscles are now quickly dissolved. Therefore all the intermediary body must have been united to the red corpuscles during the fifteen minutes' exposure at 45° C. Another demonstration of this is made as follows: If just enough red corpuscles, heated immune serum, and fresh normal serum are mixed at 0° C. in the proportions required to saturate all the affinities and to leave nothing over, on removing the corpuscles it will be found that all the complement is in the supernatant fluid, and all the intermediary body is attached to the corpuscles. This indicates that the affinity of the intermediary body for the receptor of the corpuscle is greater than its affinity for the complement, and also shows that at 0° C. the complement and intermediary body can exist side by side without combining.

The foregoing are the fundamental facts concerning the mechanism of hæmolysis, and the facts themselves are generally accepted. However, there are those who oppose the theory advanced by Ehrlich in explanation, contesting it on various grounds. For instance, by some it has been thought that the intermediary body acts after the manner of a mordant, simply modifying the cell so that it absorbs the complement, and all the features of hæmolysis are considered manifestations of physical rather than of chemical action. Nevertheless, at the time of writing it has been possible to fit all the facts that

have been developed into accord with the theory, and there is no question that the theory has been of immense value in giving a ground from which to proceed in new investigations of the laws and processes of immunity. In defending the theory, however, it has been found necessary greatly to amplify and modify the original simple conception stated in the preceding paragraphs; and, as this process is still going on, it will be impossible here to give a complete account of all the changes so made. Considering each by itself, we shall make an attempt to give the chief facts concerning the two agents in the hæmolytic process.

The Intermediary Body.—This factor in the cytolytic process has had an unfortunately large number of names applied to it, leading to much unnecessary confusion. Immune body and amboceptor have already been mentioned and explained. French writers often use the term, *substance sensibilisatrice*, with the view that its action is to prepare the corpuscle for the action of the complement. Rarely used now are the terms *fixator*, *desmon*, and *copula*. In general the name "intermediary body" (German, *Zwischenkörper*) is to be preferred, unless we are dealing with a specific substance obtained by immunization, when the term "immune body" may be used.

Its exact nature is totally unknown, for it has not been found possible to isolate it from other constituents of either serum or blood corpuscles. The fact that it is generally deprived of its action at about 70° C. would suggest that it is either a form of proteid or is combined with one. However, thermolabile intermediary bodies have been described; like the complement they are destroyed at a lower temperature. The intermediary body does not seem to develop an affinity for the complement until it has first combined with the cell.

In immunization the body is formed in large quantities, much as is the antitoxin. As a rule the greater the difference in the nature of the animals used the greater the activity of the resulting serum. Rapid absorption of large quantities of corpuscles is also desirable, to which end the blood is usually diluted with an equal quantity of 0.75-per-cent. salt solution and injected intraperitoneally. Immunization with either the stroma of red cells, or laked blood free from stroma, gives rise to hæmolysins; but pure hæmoglobin does not have as marked an immunizing power (Ford and Halsey). Ehrlich explains the formation of the immune body on the same basis as the antitoxin formation is explained. In its ordinary processes of nourishment each cell must combine with proteid molecules so large that in comparison with them the toxin molecules are small indeed. Such giant molecules cannot be used by the cell as they are, but are made available by means of a ferment-like process which splits them up into smaller fragments. This act is pictured as being accomplished by a group attached to the cell, which has one arm with affinity for the proteid molecule and another for the ferment (see No. 8, Fig. 5168). In this way the proteid molecule and the ferment are united in order that the proteid may be acted upon. It will be seen that this is merely an amplification of the idea of the toxophore group of the toxin, which is attached to the cell by the haptophore group, in order that it may produce its injurious effects. In hæmolysis the red corpuscle is considered in the place of the proteid molecule, and in immunization against red corpuscles we simply have large quantities of such "side chains" as have this double affinity for corpuscle and ferment, cast off in numbers into the plasma. These side chains, then, are the intermediary bodies, which by the nature of their affinities are able to unite the complement to the red corpuscles and to accomplish their destruction.

Normal serum may contain bodies with the same properties as the immune bodies. For example, dog serum has normally considerable hæmolytic action on guinea-pig corpuscles, and human serum on rabbit corpuscles. That this is due to the action of a true intermediary body is shown by the fact that when the serum is heated and the dog complement is destroyed, normal guinea-

pig serum when added will furnish complement and hæmolysis will occur. This also indicates that one particular intermediary body may unite with more than one sort of complement, for in this instance guinea-pig complement has taken the place of dog complement, and has united with amboceptors from dog serum. So far as we know, all varieties of animals may produce hæmolytic amboceptors. Noguchi has demonstrated their presence, both normally and after immunization, in both vertebrates and invertebrates.

It is to the immune body that the specific action of immune sera is due. This may be shown by placing both chicken and guinea-pig corpuscles in a drop of serum from a rabbit immunized against chicken corpuscles. The nucleated corpuscles of the chicken can be readily distinguished from the corpuscles of the guinea-pig, and it will be found that they undergo hæmolysis, while the guinea-pig corpuscles do not. It may also be mentioned that in this process the nuclei of the corpuscles are not dissolved, only the cytoplasm containing the hæmoglobin being noticeably affected.

On the other hand, it is possible for a serum to contain at the same time a large variety of hæmolytic amboceptors. These may be present normally, in which case the serum has the power to dissolve many varieties of corpuscles; or the same effect may be obtained by immunizing the animal with several varieties of blood at the same time. It has been shown that here we have not one amboceptor capable of uniting with all the varieties of corpuscle, but rather there is a special amboceptor for each variety. If one is removed by saturating with one sort of red corpuscle, the serum can still dissolve all the other sorts.

Another interesting feature of the immune body is that animals may be able to produce a body hæmolytic for other individuals of their own species; for example, a goat immunized against the corpuscles of another goat may have its serum become hæmolytic for the corpuscles of that particular goat. Such a lysis is called *isohæmolysis*, as contrasted with the *heterohæmolysis* formed when animals of different species are used. Of great importance is the fact that an *autolysin*, that is, a body causing hæmolysis of the corpuscles of the animal providing the serum, has not been obtained, although many experiments have been made to this end. It can be readily understood what serious results would promptly arise if such autolytic bodies were formed, and it has naturally been suggested that such a condition may exist in certain instances of auto-intoxication. In various diseases, moreover, Eisenberg found that *isoagglutinins* were present in very variable quantities, yet there were no instances in which the individual's serum was hæmolytic for his own blood. It must be admitted that at present the reason for the absence of autolysins is not satisfactorily explained.

The time required for the development of immune bodies varies greatly, as also does the time of persistence after immunizing injections are stopped. In some instances hæmolysins may be found as soon as a day after injection of corpuscles for the first time, and they are usually present in a week. In certain experiments of Ehrlich the time when maximum activity of the serum was reached varied from seven to fifteen days.

Bordet and other French observers have claimed that the union between amboceptor and corpuscle is not chemical but purely physical, but this contention seems to have been quite completely answered by Ehrlich and his followers. Ehrlich illustrates the resemblance of the reactions of intermediary bodies to known chemical substances by a comparison with diazo-benzaldehyde. By means of the diazo group the benzene radical may be united to one set of substances, such as phenols, aromatic amines, etc., while by the aldehyde group a different set of substances can be combined, including ammonia radicals and HCN. Thus by having the diazo-benzaldehyde as an intermediary body, phenol and HCN can be united, the phenol in this case assuming the place of the red corpuscle, and the HCN the place of the complement.

In any event it seems certain that the union of the immune body is with the stroma alone, and as physical means have been found inadequate to cause the liberation of the hæmoglobin it is apparent that some chemical change results.

Of the two combining portions of the amboceptor, the one that has an affinity for the complement is referred to as the *complementophile* group, while the one that unites with the cell is called the *cytophile*; or, in the case of hæmolysis, as the *hæmophile* or *hæmotrophic* group. It seems probable that there are also intermediary bodies that have several combining groups, and are therefore not amboceptors, but triceptors, quadriceptors, etc.

By those who consider phagocytosis of particular importance in all processes of immunity, the observations of Savtchenko, that immune serum causes the phagocytes to engulf corpuscles with great readiness, is esteemed of much significance. This increased phagocytosis is manifested by leucocytes either in the body or in the test tube, and may explain, at least in part, the increased phagocytosis observed in many diseases. It seems to be due, according to the observations of Hektoen, to an accumulation of specific *opsonins* in the blood; opsonins being those substances which render bacteria, corpuscles, and other cells susceptible to phagocytosis; they seem to be quite different from the immune bodies.

Immune bodies are capable of transmission from mother to foetus, although there is no transmission from the male parent. A rabbit immunized before or during pregnancy to certain corpuscles may give birth to young possessing similar immune bodies, and it is possible for immune bodies to be transmitted by the milk. Normally existing hæmolytic and agglutinating properties may be transmitted from mother to foetus, but they do not necessarily agree in proportion in the blood of each; but they are usually less in the foetus.

Complement.—Because of its property of causing solution phenomena in cells, whether corpuscles or other kinds, complement is generally considered as of the nature of a ferment, and this is supported by its susceptibility to heat, which is much the same as that of the known proteolytic enzymes. Many chemical agents, such as ten-per-cent. HCl, also destroy complements. Furthermore Delezenne has shown that the union of trypsinogen and enterokinase in the intestine, that results in the production of the active proteolytic ferment trypsin, is of exactly similar nature to the union of complement and immune body. On the other hand, after hæmolysis of red corpuscles no bodies are found that agree with those produced by either tryptic or peptic digestion, and the stroma is not ordinarily dissolved, but is deposited at the bottom of the test tube as a sediment, still retaining some of its original form. In solution of red corpuscles by the known proteolytic enzymes the hæmoglobin is attacked and much altered, while it is unaffected in serum hæmolysis. Again, the hæmolysin differs from a ferment, in that definite quantities of complement dissolve definite quantities of corpuscles, and do not have unlimited action as do the ferments; therefore it would seem that the complement enters into combination in the reaction in a way that ferments do not do.

The origin of the complement is unsettled, although there is much reason to believe that the leucocytes are one source, and perhaps the chief one. The complement content of peritoneal fluid seems to be increased if many leucocytes undergo dissolution in it, and this fact was the basis of the idea of a bactericidal substance, *alexin* (Buchner), that the leucocytes secrete. Ehrlich seems to have demonstrated that this alexin is the same as the immune body and complement, and not a single substance that by itself destroys bacteria. Aseptic inflammatory reactions have been found to increase both the bacteriolytic and hæmolytic complement of the blood, although it cannot be demonstrated that the exuded leucocytes are rich in complement. It has also been found that the complement content of the blood in disease va-

ries often in direct ratio to the amount of leucocytosis. Removal of the spleen does not prevent either the presence of complement or the formation of immune bodies in experimental animals (Levin). Complement is present in the serum of cold-blooded animals.

Undoubtedly there is more than one sort of complement, although at first Ehrlich thought that the complement was one and the same for all cytolytic processes. In some sera saturation of all the complement possible with one variety of amboceptor still leaves the serum containing complement that can dissolve corpuscles when the proper amboceptors are supplied. Again, sera have been found to possess complements with varying resistance to heat, some being indeed quite thermostable. In one serum, for example, immunized against a mixture of swine, sheep, and ox blood, Wendelstadt found that the complement for swine blood was more resistant to heat than that for ox or sheep blood, while the latter resisted HCl more. Normal horse serum was shown by Ehrlich to contain two complements; one specific for rabbit corpuscles, the other for guinea-pig corpuscles, which could be separated by filtering through a Pukall filter, as the guinea-pig complement alone passed through. This variability in filtration of complement indicates that the size or consistency of the molecules is not dissimilar to that of the enzymes, which are also variously held back by filters. Some complements have been found to diffuse through animal membranes, while others do not. It therefore seems that complement is not, as was at one time believed, a single, non-specific substance, but complements may be as numerous and as various as the intermediary bodies. However, one thing seems proved, namely, that the complement is not developed through the process of immunization, but is a constant constituent of the normal serum, although greatly fluctuating in quantity. In immune serum, as a rule, the amount of complement is inadequate to saturate the immune bodies present. As before mentioned, this deficiency may be met by adding serum from animals not immunized—serum which contains complement. As a rule the normal serum should be from an animal of the same species as the immune animal, but it is a remarkable fact that a proper complement may be obtained for immune serum of one animal from an animal of an entirely different species. For example, serum of a dog immunized against the corpuscles of a guinea-pig, after being rendered inactive by having its complement destroyed by heat, may be again activated by addition of normal guinea-pig serum; that is, the guinea-pig complement will unite with the dog immune body as well as will the complement from the dog.

Another important fact concerning the varieties and nature of complement has been furnished by Kyes, who demonstrated that red corpuscles may contain within themselves intracellular complements, *endocomplement*. Of equal significance is the related observation that *lecithin* will act as a complement for cobra poison. That a definite substance of known chemical composition may act as the complement is an important step, although *lecithin* must be more allied to thermostable complements than to thermolabile complements, which are the ones seemingly of most importance.

There are two groups in complement: one of which is united to the immune body, therefore a haptophore group, and another that acts upon the cell to which it is anchored, and called the *zymotoxigenic* group. This latter is analogous to the toxophore group of a toxin. As a matter of fact a complement is a toxin for the cell it may attack. As might be expected, therefore, just as toxoids are formed by degeneration of the toxophore group of the toxin, so also *complementoids* are formed by the degeneration of the *zymotoxigenic* group of the complement.

As before mentioned, the affinity between complement and intermediary body is less than between intermediary body and cell receptor, therefore the latter union occurs first. If the amount of intermediary body is largely in excess of the amount of complement the hæ-

molysis is greatly interfered with, because the excessive intermediary bodies unite with the complement; and as the cell receptors have all been at once occupied by intermediary bodies, the complement cannot become attached to the cell, since intermediary bodies do not unite with each other. This blocking off is referred to as *deviation of the complement*.

Regeneration of complement after it has been exhausted takes place in a short time. In rabbits whose serum was deprived of complement by injecting goat corpuscles until the complement had all been absorbed by them, it was found that complete regeneration may take place in from two to four hours.

Although the complement is the normal, constantly present constituent of the blood that probably protects the body against bacteria and other injurious agents, yet it is also capable of being harmful to the cells of its own creator. Snake venoms, for example, seem to owe their poisonous properties to the presence of large numbers of amboceptors of various sorts, and therefore to produce their violently injurious effects they require the action of complement, which is furnished by the poisoned individual for his own destruction. It is probable that there are other conditions in which the complement is an agent of harm rather than of protection.

The amount of complement in the serum of an individual varies in health, and even more so in disease. In phosphorus poisoning the power of the serum of the rabbit to destroy guinea-pig corpuscles is lost, because the corresponding complement is absent. Longcope claims that complement for typhoid and colon bacilli is decreased in many chronic diseases, which may account for terminal septicæmia. Alcoholism is also said to reduce the complement of the blood of animals. Undoubtedly the fluctuation of complement content of the blood is an important factor in determining susceptibility to infection.

An indication of how purely chemical is the union between the various substances implicated in hæmolysis is the observation by Hektoen that ions of Ca, Sr, Ba, and SO₄ combine in such a way with complement that it is unable to unite with the immune body, and thus they prevent hæmolysis. These inorganic substances seem to saturate the affinity of the haptophore group of the complement in the same way that amboceptors do.

Antihæmolysin.—Just as an antitoxin can be produced by immunizing cells against the toxins that injure them, so by immunizing the blood corpuscles against hæmolytic serum an antihæmolytic serum can be obtained. If heated serum is used in immunizing, an anti-immune body is obtained, that acts by combining with the cytophile group of the intermediary body and thus preventing the intermediary body and the corpuscles from uniting. If there are several intermediary bodies in the injected serum, antibodies may be obtained that are specific for each. These antibodies seem to be the receptors of the red cells that unite with the intermediary body in producing hæmolysis.

By immunizing against normal serum, whether heated or not, *anti-complement* is obtained which also is specific. Ehrlich has shown that this anti-complement acts by combining with the haptophore group, thus preventing the complement from being anchored to the cell by the intermediary body. Such anti-complement does not unite at all with the intermediary body, which remains in a condition capable of taking up fresh complement if it is provided. Again, resembling the production of antitoxin with toxoids, anti-complement can be obtained by immunizing with complementoid.

Not only can *anti-heterolysins* be obtained, but also *anti-isolysins*, if serum hæmolytic for blood of an homologous animal be used in immunizing. Since during normal conditions of life red corpuscles are continually undergoing dissolution, it may be that in every body there really develop autolysins, which are prevented from causing extensive destruction of the corpuscles by the production of *anti-autolysin*. Besredka seems to have demonstrated the presence of such antibodies in normal

serum, and suggests that such self-immunization may be an important process in protection of the body. In this connection it may be mentioned that there seem to be antiferments normally present in the blood that are perhaps of importance in preventing self-digestion of the tissues during life by the ferments of the body itself.

Agglutination in Relation to Hæmolysis.—The well-known agglutinating reactions of bacteria can be duplicated with red corpuscles. As with bacterial agglutinins the agglutinin seems to be, in Ehrlich's terms, a uniceptor; that is, it has but one group with affinity for other substances, as is the case with the toxins. Agglutinins for corpuscles are found to varying extent in normal serum, as well as in serums specifically immunized against the corpuscles. Heating at 55° C. does not destroy the agglutinin, and in this way the agglutination can be observed independently of the hæmolytic processes. Agglutination also occurs at temperatures approaching freezing, when hæmolysis is inhibited. Agglutinated red corpuscles collect in rouleaux and clumps that unite with considerable tenacity, so that ordinary shaking will not break them up. In hæmolytic immune serum this agglutination precedes the hæmolysis, but the two processes are quite unrelated. Normal serum may contain agglutinins and not be at all hæmolytic, and the converse is also true. The mechanism of agglutination is not understood, but it is suggested that some chemical change in the substance of the corpuscle renders the surface adhesive, or that some physical change in surface tension accounts for the coaptation and adhesion of the corpuscles. As agglutination occurs in corpuscles that have been fixed in formalin or sublimate, it is probably not the protoid of the corpuscle that is affected, but the other ingredients of the stroma, of which lecithins and cholesterin seem to be the chief. Flexner and Noguchi found that if ricin, an agglutinator, was allowed to act for two or more hours it is still possible then to produce hæmolysis by serpent venom, but the stroma remains at the bottom as a white, conglutinated mass. From this it appears that agglutination brings about a kind of coagulation of the stroma.

Agglutination of the corpuscles during life may be of some pathological importance, for such masses of agglutinated corpuscles could readily produce capillary thrombi and emboli, which, if widespread, might create much disturbance. Many bacteria produce substances that are agglutinative for human red corpuscles, among them being typhoid, pyocyaneus, and staphylococcus. Flexner has found in typhoid fever thrombi that seemed to be composed of agglutinated red corpuscles, almost free from fibrin and leucocytes. Probably many of the so-called "hyaline thrombi" found frequently in infectious diseases are really composed of agglutinated, partly hæmolyzed red corpuscles. Pearce has found that agglutinative serum when injected into dogs causes widespread necrosis of the liver.

Agglutination is also produced by certain vegetable poisons, including ricin, abrin, and croton, and these have been found to produce thrombi of agglutinated red corpuscles. Of these substances ricin alone, although strongly agglutinative, has no hæmolytic action, showing the independence of the two processes. Snake venom, like most hæmolytic substances, produces marked agglutination, and here also the agglutinin is distinct from the hæmolysin.

(3) HÆMOLYSIS BY BACTERIA.

Both pathogenic and non-pathogenic bacteria produce hæmolytic substances that are excreted into the fluids in which they grow. During many infectious diseases marked hæmolysis occurs, especially in those with septicæmia. After death the hæmoglobin of the blood goes into solution, and the resulting staining of the walls of the blood-vessels, and later of the tissues everywhere, is generally familiar. In the post-mortem hæmolysis probably the putrefactive organisms are chiefly concerned, although it is marked a very short time after

death in many cases of septicæmia, particularly when the infecting organism is the streptococcus, and here probably the pathogenic organism is the chief cause of the hæmolysis. The hæmolytic action of bacteria can be studied both *in vitro* and *in vivo*. Among the best known are *tetanolysin*, *pyocyanolysin*, *typholysin*, *staphylolysin*, and *streptocolysin*, as they have been termed. Of these the case of pyocyanolysin is questionable because it has been described as resisting heat over the boiling point, and Jordan seems to have proved that the hæmolysis is ascribable to the alkalinity that this organism produces in culture media. Other bacterial hæmolysins are, however, destroyed by heat at 70° C. for two hours; that is, they are altogether different from ordinary cellular hæmolysins. G. Ruediger shows the following differences between streptocolysin and the hæmolysins of serum: Streptocolysin is not destroyed at 65° C. for one-half hour, and therefore is different from complement. When destroyed by heating to a higher point it cannot be reactivated by the addition of complement, thus differing from intermediary body. It is also different from intermediary body in that it does not combine with corpuscles at 0° C.; on the other hand it does combine at 6° C., but does not exert any hæmolytic effect until the mixture is raised to a higher temperature. This last observation indicates that the streptocolysin is similar in nature to the toxins, which exhibit the same phenomena. Other observations indicate that its structure is the same as the toxins, namely, a toxophore group and a haptophore group. In other words, streptocolysin is simply a toxin for red cells, which acts like bacterial toxins for other cells by joining directly to the cell receptors without the intervention of any intermediary body. As a similar structure has been shown for staphylolysin and tetanolysin, it is probable that the bacterial hæmolysins are all merely toxins with a particular affinity for red cells.

Secondary anæmia of the infectious diseases is probably to be explained largely by this hæmolytic property of bacterial toxins. Hæmoglobinuria also may be produced in the same way. Intravenous injections of filtrates of the saphrophyte, *B. megatherium*, will produce hæmoglobinuria in guinea-pigs.

(4) HÆMOLYSIS BY VEGETABLE POISONS.

A number of plant poisons are strongly hæmolytic, and some of them owe their toxicity largely to their effect on the erythrocytes. One group, which includes ricin, abrin, croton, robin, and phallin, is composed of substances supposed to be proteids, and called *vegetable toxalbumins*; of these croton and phallin are most actively hæmolytic, while with the others the agglutinating action is relatively more prominent. They resemble the bacterial toxins in that immunity can be secured against them, but they resist heating to 70° (except phallin). The activity of these toxalbumins may be realized if it is mentioned that purified ricin kills rabbits in doses of 0.000001 gm. per kilo of body weight, and solutions of 0.001 per cent. agglutinate red corpuscles. According to the investigations of Ford and Abel the hæmolytic poison of the poisonous mushrooms, the phallin of Kobert, is not a toxalbumin but a glucoside. Another quite distinct group of vegetable poisons with hæmolytic properties consist of the *saponin substances*, of which there are many varieties widely distributed in the vegetable kingdom. Sapotoin of soap bark is one of the best known. They are entirely different from the toxins, being heat resistant and not giving rise to antibodies when injected; chemically they are glucosides. Apparently they produce their effect by acting on the lipoids, especially the cholesterin, of the corpuscles.

(5) HÆMOLYSIS BY VENOMS.

The hæmolytic power of venom derived from different varieties of reptiles has through recent studies been brought into the domain of biologic hæmolysis, and

the result has been not only an understanding of the mechanism by which the lethal effect of these poisons is produced, but also perhaps the strongest support of the principles of Ehrlich's theory yet offered from outside sources. At the same time a new, easily controlled medium for research in problems of immunity has been provided. The most fundamentally important fact is the discovery by Flexner and Noguchi that the hæmolytic and other toxic agents of venom are themselves true intermediary bodies. By itself venom is not hæmolytic, but it requires the presence of complement to enable it to produce hæmolysis, and as the venom contains no complement, this necessary part of the poison is furnished by the serum that contains the corpuscles. This is indeed a remarkable fact, that the active part of the serpent's poison is furnished by the victim itself, and particularly so in view of the position that serum complement usually assumes as a protector against bacteria. The existence of a widespread power against various animals implies that these venom intermediary bodies are capable of uniting with the complement of sera of varied animals, are *heterocomplementophilic*, in the language of Ehrlich's theory, and experiment shows this to be true. The probable source of these intermediary bodies is apparently in the serum of the serpents, as if they were secreted directly from the blood into the poison glands, for serum of poisonous snakes is found to possess intermediary bodies almost identical with those of the venom. The only difference is that while venom intermediary body combines with complement of nearly all serums, the serum immune body combines almost only with the complement of the serpent's serum itself (*isocomplementophilic*). Venom from cobra, rattlesnake, moccasin, and copperhead possesses in each intermediary bodies that seem to be identical in nature, although they may vary in quantity. This explains the rather remarkable fact that serum of animals immunized against cobra poison, generally called *antivenin*, will neutralize the hæmolytic and many of the other properties of the venom of rattlesnake, copperhead, and moccasin. Antivenin acts as an anti-intermediary body, and by occupying one of the haptophore groups of the venom keeps it from uniting complement and cell. In order of decreasing hæmolytic power for mammalian corpuscles come venoms from cobra, water moccasin, copperhead, and rattlesnake. These venoms are also agglutinative for all corpuscles tried, and agglutination will occur at 0° C. Exposure for thirty minutes at 75°-80° C. destroys the agglutinative property. In general, the hæmolytic power of the venoms for different sorts of corpuscles varies in inverse proportion to its agglutinative power. The hæmolytic intermediary bodies are remarkably resistant to heat, suffering but slight loss of power at 100° C. Each venom contains many intermediary bodies, seemingly different for each sort of corpuscle hæmolyzed, at least to a great part; no one sort of corpuscle can so saturate all the intermediary bodies that none is left for other kinds. After the intermediary body is attached to a corpuscle it can unite with many different sorts of complements, but only the one natural to its serum accomplishes complete hæmolysis. Leucocytes also are dissolved, and they seem to have specific intermediary bodies different from those that unite with red corpuscles, but the agglutinin for each seems to be the same. As the venom contains large amounts of intermediary bodies, when an animal is poisoned by a snake the complement is quickly taken up, and this probably explains the deficient bactericidal power of blood serum in this condition that permits the extensive infections so characteristic of snake bites. Antivenin will prevent this interference with normal bacteriolysis by occupying one of the groups of the intermediary bodies of the venom so that it cannot use up the serum complement.

The highly hæmolytic cobra venom can combine with complements contained within the red corpuscles, *endo-complement*, and so produce hæmolysis in the absence of serum complement. Kyes has shown that *lecithin* may

be the constituent of the red corpuscles that acts as the complement.

In passing it may be noted that the effects of venom on nerve and endothelial cells, which with the hæmolysis constitute the manifestations of its toxicity, are produced in the same way as the hæmolysis. Amboceptors are present that unite complement to these cells, enabling it to attack them. As certain venoms are richer in one sort of intermediary body than others, so the effects of the bite of one kind of snake differ from those of another kind, *e.g.*, rattlesnake poison is particularly endotheliolytic, and therefore hemorrhages are a prominent sequence of the rattlesnake's bite.

Red corpuscles of the frog are not hæmolyzed by venom, and those of *necturus* (mud puppy) but slightly, agreeing with the known resistance of cold-blooded animals to snake bites.

Eel serum is remarkably hæmolytic, so much so that a quantity of 0.1 c.c. per kilogram of body weight will kill a rabbit or guinea-pig in three minutes when injected intravenously. Heating at 54° C. for fifteen minutes destroys the hæmolytic action, and, unlike ordinary serum hæmolysins, the addition of complement does not restore its activity. Animals can be immunized against this serum. Introduced into the stomach, eel serum is not toxic. It can be dried and redissolved without losing its activity, but acids and alkalis readily destroy it. Mosso, who first discovered the toxicity of eel serum, called the unknown active principle *ichthyotoxin*.

HÆMOLYSIS IN DISEASE.—During health there is always going on a certain amount of destruction of red corpuscles that have outlived their usefulness; so in disease we may have to deal with either an alteration in the normal processes of blood destruction, or the introduction of entirely new processes. Although the place and manner of normal red-corpuscle destruction is not completely known, yet it seems probable that there is relatively little hæmolysis within the circulating blood. When a red corpuscle becomes damaged it seems to become more susceptible to phagocytosis, and it is picked out of the blood chiefly by the endothelial cells of the sinuses of the spleen, hæmolymph glands, and bone marrow. Within these cells it apparently undergoes hæmolysis. Eventually the resulting pigment is split up by the liver, the non-ferruginous portion forming the bile pigments, while the iron seems to be mostly withheld to be worked over into new hæmoglobin. Whenever during disease red corpuscles are more rapidly injured than they are under normal conditions, these processes of normal hæmolysis are exaggerated and we not only find the phagocytic cells of the spleen and glands packed with them, but endothelial cells elsewhere and leucocytes also take on the hæmolytic function. At the same time there is an excessive production of bile pigment from the destroyed red corpuscles, which has an undetermined relation to the so-called "hæmato-hepatogenous" jaundice. If hæmolysis is very excessive the blood pigment accumulates in other organs than the liver and spleen. When at one time over one-sixtieth part of the hæmoglobin of the blood is in solution in the plasma, it may escape in the urine, producing hæmoglobinuria.

The hæmolysis of the acute febrile diseases is readily explained by the demonstrable hæmolytic property of the products of the organisms that cause them, such as streptococcolysin, staphylolysin, etc. Perhaps at the same time altered metabolic products may also play a part, but it does not seem probable from experimental results that the thermic condition *per se* has much effect. In malaria, although the parasites enter and destroy the corpuscles in which they live, yet this alone does not account for all the blood destruction of the disease, for the amount of anæmia is quite without relation to the number of parasites to be found. There is good reason to believe that the plasmodia produce hæmolytic substances that are discharged into the serum. In the primary anæmias hæmolysis seems to be the essential proc-

ess, although the agents involved are at present unknown. Absorption of hæmolytic products of intestinal putrefaction or infection has always come in for much suspicion, without ever becoming completely established. Here also the hæmolysis seems to take place in the endothelial cells rather than in the vessels. In such a disease as pernicious anæmia there is much reason to assume that defective or abnormal hæmatogenesis is an important factor. Probably the anæmia of nephritis is the result of hæmolytic action of the retained products of metabolism, in which connection the hæmolytic properties of ammonium compounds may be recalled. In some diseases associated with anæmia it has been found that the blood serum of the patient is distinctly isohæmolytic, although isoagglutination seems to be more frequent. Such sera, however, do not seem to be autohæmolytic, at least in the test tube. The bloody fluids that can be obtained from cancers have been found to be hæmolytic, while antihæmolysin has been found in ascitic and pleural effusions. Autolyzing tissues produce hæmolytic substances.

In many forms of poisoning hæmolysis is a prominent feature; in some it seems to be the chief effect of the poison, *e.g.*, potassium chlorate and arseniuretted hydrogen. In severe extensive burns there may occur hæmolysis, and hæmoglobinuria may also result. The remarkable "paroxysmal hæmoglobinuria" is at present without satisfactory explanation as to the cause of the hæmolysis. The hæmoglobinæmia of "blackwater fever" has been the cause of much discussion as to whether the malarial parasite or the quinine is the cause, with a divided opinion resulting, although undoubtedly cases do occur in malaria without administration of quinine. After removal of the spleen hæmolysis by the hæmolymp glands exceeds that of the primitive spleen, causing an excessive destruction of red corpuscles (Warthin). This suggests that the spleen may normally dispose of some hæmolytic agent which acts either by stimulating phagocytosis or by so altering the red cells that they are particularly susceptible to phagocytosis.

The lesions produced in the organs of animals injected with hæmolytic agents are usually pronounced and quite characteristic. There is often a subcutaneous œdema, frequently blood-stained, and similar fluid may be present in the serous cavities. The fat is yellowish, and the muscles are darker in color than is normal. The spleen is usually much swollen, soft, friable, and very dark in color. The liver is usually swollen and mottled with red areas in a yellow background. The renal cortex is dark in color, even chocolate-colored, and the pyramids are comparatively light; in the urine is frequently hæmoglobin. In the lungs are often hemorrhages or areas resembling small infarcts. The blood may be thin and even distinctly transparent. Microscopically the red corpuscles are found in all conditions of degeneration, and often fused together. In the liver, besides patches of congestion, fatty changes are present if the animal lives long enough. Large phagocytic cells packed with red corpuscles are abundant in the spleen, as well as diffuse accumulations of blood, often fused, and pigment both free and in the cells. Pigment also accumulates in the renal epithelium, which also often shows much disintegration; congestion is prominent and hemorrhages into both interstitial tissue and glomeruli are frequent.

BACTERIOLYSIS.—It is not our purpose in this article to discuss the specific micro-organisms in this relation, but merely to indicate the relations of hæmolysis and bacteriolysis. Whatever has been said in preceding paragraphs about the mechanism of hæmolysis can be transcribed to apply to bacteria and bacteria-immune serum. Pfeiffer's observation of the solution of bacteria by serum of immunized animals was the precursor of the modern studies of hæmolysis and the extension of Ehrlich's theory. Indeed the chief reason for the great interest in hæmolysis lies in the understanding that whatever may be learned about hæmolytic processes can be directly applied to the processes of immunity against bacteria. Therefore we understand that in the serum of

an animal immunized against bacteria themselves, and not merely their toxins, there is present an intermediary body that is specific for the injected organism. This intermediary body attaches itself to the bacterium by one haptophore group, and with the other anchors the complement of the serum which then destroys the bacterium. Now as during immunization only intermediary bodies are produced in excess, while the complement is not increased, it often may be that defence may fail because of deficiency in the amount of complement. This possibly explains why it has so far been impossible to secure immune sera that will protect against bacteria as effectively as antitoxin protects against toxin, for with toxin no complement is required. The results of decreased complement content would be an increased susceptibility to infection, and this is seen in snake bites, when the venom uses up the blood complement and the patient often succumbs to bacterial infection after surviving the direct effects of the poison. In chronic diseases Longcope claims that in the later stages the amount of complement is much decreased, probably accounting for the occurrence of terminal septicæmias.

It is probable that hæmolytic complement is quite distinct from that causing bacteriolysis, and that complements for different bacteria can be separated from one another as well as from the agglutinins.

Welch has suggested that possibly the bacteria in their turn may develop antibodies to the tissues and fluids in which they are growing. If so, we have a reasonable explanation of the development of toxic substances with marked action on specific cells of the host, *e.g.*, endotheliolysins, leucolysins, hæmolysins; and also the peculiar manner in which bacteria often attack only certain tissues, *e.g.*, multiple septic arthritis.

CYTOLYSIS.—Red corpuscles being merely a particular sort of body cell it might be expected that lysins for other cells could be obtained in a similar manner, and such is the case. Such lysins are called by the generic term *cytolysins*, or *cytotoxins*, and are specifically indicated by the name of the cell concerned, as endotheliotoxins or endotheliolysins, hepatotoxins, nephrotoxins, etc. The lysins or toxins in this case are similar in composition to the hæmolysins, that is, an amboceptor and a complement group, and these groups are in all respects similar to the components of the hæmolysins except that the cytophile group of the amboceptor is more or less specific for certain tissue cells rather than for red corpuscles. Such cellular toxins may be obtained by immunizing the animals against the tissue which is injected emulsified into its peritoneal cavity; but, as with the hæmolysins, they may occasionally appear in normal serums of various sorts of animals. It is by no means as easy to determine the results with tissue cells as with red corpuscles, where the liberation of the highly colored hæmoglobin is easily detected. To some degree lytic changes can be observed in tissue cells under the microscope, but this is not usually very satisfactory. Another method of observation consists in injecting the immune serum into the body of an animal, and studying both the symptoms and the anatomic changes brought about in this way. The latter method has found the most general application. A disturbing element in all such experiments lies in the difficulty of securing tissue cells of one kind alone for injecting. For example, when hepatic-tissue suspensions are injected there are introduced at the same time endothelial cells, connective-tissue cells, and usually red corpuscles and leucocytes. Therefore an immune serum obtained in this way would contain immune bodies for all these cells, and it becomes impossible to ascribe any changes that follow its injection into an animal solely to effects of the hepatotoxins. While there are possible ways of avoiding many of these difficulties they have not been generally applied, and much of the earlier work is very questionable on this account. At the same time that cytolysins are formed agglutinins also appear, and agglutination of cells occurs as it does with bacteria and corpuscles. One of the earliest pieces of work in this di-

reaction was with sperm agglutinins, obtained by immunizing with sperm. Such serum, however, was not spermolytic.

It was at first believed that it would be possible to obtain immune serum so specific for a given organ or tissue that by injection of the proper immune serum a given organ could be thrown entirely out of function, but these ideas have not been realized, for immune serums as yet obtained do not show any high degree of specificity for the type of cells used in immunizing. The immune serums usually obtained do, to a certain extent, injure the specific organ, but they also often injure other organs as much or perhaps even more. Beebe claims to secure more specific sera by immunizing with the nucleo-proteids of organs, but at the time of writing, this work has not been satisfactorily corroborated, Pearce and Jackson being unable to confirm it. In view of the elementary condition of cytolytic investigations, and the afore-mentioned sources of error in much of the work that has already been reported, I do not feel justified in this article in more than briefly discussing the specific results so far obtained. It should also be mentioned that recently some investigators who have used care in avoiding hæmolysins, etc., in preparing specific sera have not been able to obtain as marked results as had been earlier reported.

Leucocytolytic Serum.—This may be obtained either by immunizing with leucocytes obtained from exudates or from the blood, or by using emulsions of lymph glands. The latter method introduces so many cells besides the lymphocytes that it is not desirable. Specific leucocytolytic sera agglutinate leucocytes and produce observable morphologic changes, in the way of solution of the cytoplasm and cessation of amoeboid movements. Of the leucocytes the large granular cells seem most affected and the lymphocytes least. When injected into the peritoneal cavity such serum causes an apparent initial leucopenia, and later a decided leucocytosis in the peritoneal fluid. Corresponding with this, if bacteria are injected at the same time as the serum, resistance is found decreased, but later it is much increased. Such serum also contains anticomplement, according to Wassermann, indicating that the injected leucocytes contain complement. Leucotoxin obtained by immunizing against lymphatic tissue is very thermolabile, being destroyed by 55° C. for thirty minutes, and the serum can be only partially reactivated by the use of fresh serum. Undoubtedly leucotoxic amoebocytes are present in many normal sera, and their presence in the serum of certain cold-blooded animals and in venom has already been shown.

Endotheliolytic Serum.—Every attempt at immunizing an animal with any sort of fixed tissue must of necessity involve the injection of endothelial cells as well as those specific to the tissue studied. Therefore it is possible that cytotoxic serum so obtained will contain endothelial toxins and so complicate any results of *intra vitam* experiments. There is every reason to believe that endotheliolytic substances are produced in this way. Ricketts found that serum of animals immunized against lymph glands was toxic to endothelial cells, which was indicated by hemorrhages at the point of injection, and marked desquamation of endothelium when the injection was made into a serous cavity. In snake poisoning the extensive hemorrhages are also due to an endotheliolytic principle, called by Flexner *hæmorrhagin*. This is destroyed by heating at 75° C., and is particularly abundant; in fact, the chief toxic agent in rattlesnake venom.

Lymphatolytic Serum.—This serum has been studied recently by Ricketts and by Flexner, immunizing animals with lymph glands. As might be expected from the nature of the injected glands the resulting serum contained endotheliotoxin, leucotoxin, hæmolysin, hæmagglutinin, leuco-agglutinin, and precipitins. When injected into animals this serum had a marked effect upon the spleen and lymph glands, producing great enlargement of these structures, which were also congested.

The bone marrow was also somewhat affected, and when marrow was used in immunizing, the *myelotoxic* serum produced marked proliferative changes in the lymph glands as well as in the marrow. The changes produced in the leucocytes were the same as those described for leucotoxic serum, indicating that the different forms of leucocytes can combine with immune bodies produced against lymphocytes. Leucotoxic substances are said to be produced in the blood of leukæmic patients who have been treated with x-rays (Capps and Smith).

Nephrolytic Serum.—It has been claimed that if a kidney is destroyed by ligating its vessels or ureter the remaining kidney develops serious degenerative changes, which are not present if one kidney is entirely removed. This has been attributed to the development of nephrotoxic substances produced in reaction to the absorption of the injured renal tissue that has been left in the body. Other methods of renal injury have been thought to produce similar effects, and serum of animals with kidney disease was said to injure the kidneys of normal animals. From this basis it has been thought to explain the progressive nature of the chronic nephritides as the result of nephrotoxins produced through the absorption of the injured cells, and which nephrotoxins injure still other cells. Such a process, however, involves the production of cell toxins in an animal toxic for its own cells, that is *autocytotoxins*; and as it has so far been practically impossible to produce autolysins of other sorts, it is not altogether probable that the kidney is an exception. Furthermore, Pearce was unable to produce *isonephrotoxins*, and could not corroborate the results said to have been found in the remaining kidney after ligating the vessels of the other. He did obtain an active *heteronephrolysin*, but also found that immunization with liver produced just as actively nephrolytic serum as immunization with kidney.

Neurolytic Serum.—Even so highly specialized cells as those of the nervous tissue seem to produce a reaction with the formation of immune bodies. Perhaps because any symptoms produced by action on the nervous system are so readily detected, and because of the advanced condition of our knowledge concerning the minute structure of ganglion cells, the results obtained with neurolytic serum have been particularly striking. Perhaps the most positive results are those of Ricketts and Rothstein, who found that serum of rabbits immunized against the brains or cords of guinea-pigs was highly toxic, when injected into the vessels of guinea-pigs, causing death with various symptoms only explainable on the assumption of nervous lesions. Microscopically the ganglion cells showed marked changes in those animals that survived the injection long enough. All the results so far obtained have been with heterogeneous serum. Venoms, particularly that of cobra, possess strong neurolytic substances, that are the chief toxic agents in most of the venoms (the rattlesnake excepted). This neurolysin can be removed by saturation with nervous tissue from the hæmolysin, and conversely the hæmolysin can be removed by saturating with red corpuscles, thus corroborating Wassermann's experiments with tetanus toxin and supporting Ehrlich's theory.

Thyrolitic Serum.—The report of Portis indicates that after removal of all hæmolysis as a factor there do occur changes in the nature of excessive absorption of colloid, and proliferation after the order of that seen in regeneration. However, the clinical picture of thyroidectomy was not produced in any case, and the anatomic changes were not great. Beebe has secured an antiserum by immunizing with thyroid nucleo-proteid which has been used with apparent success in the treatment of exophthalmic goitre. MacCallum could not obtain an anti-serum specific for the parathyroid.

Numerous reports may be found indicating attempts with varying success to obtain sera toxic for other tissues. Among them may be mentioned *epitheliolysin* (for ciliated epithelium), *spermatotoxin*, *hepatolysin*, *cardiolysin*, *splenolysin*, and *syncytiolysin*. Attempts at the production of immune serum with adrenal by Ab-

bott resulted only in a serum with great hæmolytic power, but with no particular effect on the adrenal. The principle in all is the same, but the results as a whole are not now in a state to warrant extensive consideration. In general, it can be said that it has not been found possible in this way to throw out of function one particular organ, with or without involvement of other structures. It must be borne in mind that we can have grave functional disturbances without corresponding anatomic alterations. There is no reason known why a group of receptors of essential importance to the functional manifestations of the cell may not be quite independent of vegetative functions; and with impairment of these alone there need be no visible cell changes.

H. Gideon Wells.

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HARROGATE.—Harrogate is situated in Yorkshire in the central portion of England, midway between the Irish Sea and the German Ocean, four and one-half hours by rail from London. Its reputation depends not only upon its waters but as well upon its climate, which is dry, invigorating, and with an atmosphere of remarkable purity. It has an elevation of 260 to 600 feet above sea-level. The town consists of "Low" and "High" Harrogate, High Harrogate possessing the more bracing climate, while Low Harrogate is more sheltered and enjoys a reputation as a winter resort. There are fewer rainy days, it is said, than at most of the other English health resorts. The season is from May to September, though the spa is open at other times of the year.

There are about eighty different cold mineral springs at Harrogate, most of them containing sulphur in the form of sulphuretted hydrogen and sulphide of sodium, varying greatly in strength and proportion of the constituents. The most popular spring and the one generally used for drinking is the "Old Sulphur Spring" in the Royal Pump Room, which contains about 0.07 of sodium sulphide and 37 volumes of sulphuretted hydrogen per litre; it also contains 12.7 of common salt and 0.09 of barium chloride, which latter substance is said to act as a heart tonic and to obviate any depressing effects of the sulphur. The "Montpellier" is the strongest in sulphur, estimated to contain 0.2 per litre of sodium sulphide with no sulphuretted hydrogen. The Starbeck wells, on the contrary, are weak in sulphur and are used for baths.

There are also iron springs, and of these the famous "Kissingen Well" contains 0.13 of carbonate of iron, 10.0 of sodium chloride, and 1.2 calcium chloride per litre, and the "chloride-of-iron well" contains 0.19 of chloride of iron, 0.16 of carbonate of iron, 2.5 of chloride of sodium, and 0.07 of chloride of barium per litre. There is also the sulphate-of-iron water from the so-called "alum well" in the "bog field," containing ferrous sulphate, ferric sulphate, aluminum sulphate, calcium sulphate, and magnesium sulphate, about 1.0 per litre of each.

The waters of Harrogate are applicable to about the same class of cases as are treated at Homburg and Kissingen, although the waters of these two latter spas contain no sulphur, and Kissingen contains no iron. Chlorosis, anæmia, hepatic disorders, lead and mercurial poisoning, chronic dyspepsia, constipation, obesity, cer-

tain skin diseases, functional uterine disorders, scrofula, chronic gouty and rheumatic conditions, and bronchitis are all said to be benefited by the use of these waters. It is well to remember that the climate, regular mode of living, freedom from care, and the general simplicity of life add much to the effect of the waters, and this is true of all water cures.

The sulphur waters, of which the "Old Sulphur Spring" stands first in importance,—the chlorides it contains giving it a special therapeutic value,—are employed both for drinking and in baths, particularly for drinking, and are most useful in functional hepatic disorders, digestive disturbances, constipation, etc., gout, rheumatism, chronic lead poisoning, and externally in eczema and psoriasis. The chalybeate waters are employed in anæmia, albuminuria, convalescence from prolonged or severe illness, scrofula, and also in chronic rheumatic arthritis.

The contraindications to the use of these waters are organic diseases of the heart, blood-vessels, liver, and kidneys, and in cases of asthma, insomnia, and neurotic conditions generally.

The bath establishments are modern and complete. The new Royal Baths, erected ten years ago at a cost of \$600,000, are called "one of the sights of Europe." There are special attendants for administering the "Aix douche" as is done at Aix-les-Bains, which are much employed in chronic gouty and rheumatic cases.

The accommodations are good and abundant. The hotels and residences are built around an open common of two hundred acres; the sanitary conditions are excellent, and there is an abundant supply of pure, soft water. The amusements are music, tennis, golf, cycling, cricket, and hunting. The scenery about Harrogate is very attractive, affording many interesting excursions.

Edward O. Otis.

HEART-BLOCK.—By this term is meant that condition in which, owing to some interference with the muscular connection between the auricle and the ventricle (the auriculoventricular bundle of His), there is an arrest or "block" of the stimulus of contraction on its way from the auricle to the ventricle. The result of this is that the ventricle misses a beat or perhaps several, while the regular systole of the auricle is continued.

Heart-block may be *partial* or *complete*. In the former there is a definite ratio between the contraction of the ventricle and that of the auricle; in the latter, when the block is complete, the rhythm of the ventricle and that of the auricle are entirely independent of each other, the ventricular rate being the slower. In partial block the ratio of the auricular to the ventricular rate is 2 : 1, 3 : 1, or even 4 : 1.

The question is still unsettled whether the heart-beat as a whole is due to muscular or to nervous impulse. The older theory, the *neurogenic* (based especially on the work of Volkmann and Bidder), placed the source of the heart's action in the intracardiac ganglia, which were assumed to be connected into a co-ordinated mechanism for the purpose of obtaining the proper sequence of the contractions of the individual heart segments (the venous end, the auricle, and the ventricle).

The *myogenic* theory attributes the origin of the normal stimulus, its rhythmic character, and its conduction through the heart, exclusively to the muscular elements of the organ. The action of the extracardiac heart nerves and of certain heart poisons are referred to a direct influence upon the heart muscle. For several years the neurogenic theory was the favorite; but of late, and particularly since the discovery of the "bundle of His," the myogenic theory has received much more support.

According to the teachings of those holding the myogenic theory, the regular heart action is the result of the combined effect of the four chief functions of the heart muscle, viz., automatic stimulation, irritability, capacity of transmitting the motor stimulus from one muscle cell to another, and muscular contractility. It is at

once evident that the disturbance of one of these chief functions will be followed by a typical interference with the summation of the remaining functions. The degree of the capacity to transmit the motor stimulus from one muscle or cell to another, or the conductive power, may be measured by the interval of time between the auricular systole and the ventricular systole. Since the motor stimulus starts from the sinus venosus and passes by way of the auricle and ventricle to the apex, it is evident that a certain time must elapse between the successive contractions of each of these segments. The transmission is most sluggish at the transition from one heart segment to another, most distinctly so at the transition from the auricle to the ventricle. It must furthermore be taken into consideration that the conductive power, as well as the other heart functions, is dependent upon the phase of the cardiac cycle. In the "refractory" phase—the systole—the heart muscle is not capable of conduction, nor is it susceptible to extra stimulation; in other words, the conductive power is destroyed by each systole, and gradually revives during the diastole. If the conductive power is lessened from any cause, such as, for instance, asphyxia, vagus stimulation, digitalis, etc., then the interval between the auricular systole and the ventricular systole is necessarily increased. This interval may become so long that the ventricular systole sets in only a short time before the next following auricular systole, so that apparently there is an inverse rhythm in the heart contraction, from ventricle to auricle. When the conductive power is still poorer, the interval may become interminable, meaning that the stimulus is not transmitted. Thus one cardiac contraction is left out, giving the muscle time for recuperation and accumulation of an improved conductive power.

Until 1893 it was believed that the auricles and ventricles were independent muscles, separated by a fibrous ring. In that year, Wilhelm His, Jr., described what has since been known as the "auriculoventricular bundle of His." The subject attracted little attention at the time, but the researches of Retzer, Bräunig, Humblet, Hering, Tawara, Keith, Erlanger, and others have not only confirmed the existence of the bundle, but also made more clear its histological structure and physiological importance. This muscular bundle represents the only muscular connection between the auricles and ventricles. According to Dock (*Detroit Medical Journal*, October, 1907): "Retzer found the bundle about 18 mm. long, 2.5 mm. wide, and 1.5 mm. thick. According to Tawara, that is only part of an extensive series of fibres, beginning in the septum of the auricle, forming a node just above the fibrous septum and later dividing into two legs which pass down the ventricular septum and, breaking up into fine arborescent fibres, the fibres of Purkinje, pass off to all parts of the ventricle, under the endocardium, at first surrounded by connective tissue, finally fusing with the muscle fibres. The most recent investigator, Fahr, makes the bundle 40 mm. long, coalescing with the heart fibres at both ends. Keith rather confirms Tawara's findings, but he also finds that in mammals the conducting fibres are more like muscle fibres, whereas in lower animals he finds differentiated fibres beginning in the veins and running into the auriculoventricular bundle."

From the investigations of His and Hering it was learned that when a small knife is introduced into the left auricle of a rabbit, so as to perforate the septum, it is noted that the ventricle and auricle keep on pulsating after the injury, but each part with a rhythm of its own. This auriculoventricular allorhythmia, however, occurs only in those cases in which the bundle of His has been injured or severed; whereas destruction of other parts of the septum is never followed by this phenomenon. Although the remaining anatomical connection between the auricle and ventricle may be preserved, the functional connection is completely severed by a division of the bundle of His. The ventricles beat automatically, and in a slower rhythm than the auricles,

both, however, pulsating regularly; and neither spontaneous nor artificial stimuli pass from one part of the heart to the other. Hering's experiments proved the notable fact that His's bundle possesses the function of conducting stimuli from the auricle to the ventricle. Hering arrived at the conclusion that this conduction is purely muscular and not nervous, basing his opinion upon the supposition that the muscular bundle has no other known function, and that a conduction by way of both muscle and nerve seems hardly probable.

His (*Deutsches Arch. f. klin. Med.*, 64, 1899) enumerates three possibilities for the origin of heart-block: (1) an abnormal condition of the ventricular muscle; (2) changes in the muscular constituents which transmit the stimulus to the ventricle; (3) abnormal influences on the part of the vagus nerve, which may also be combined with abnormalities of the muscle. Heart-block may result in consequence of injury to the ventricular muscle, retarding or inhibiting its conductive or contractile power. The damage may be either temporary (over-distention, anæmia, etc.) or permanent (degeneration, inflammation). The second possibility refers to the muscular bundle; and it has been shown that when this bundle is destroyed the auricles and ventricles begin to beat independently of each other, and at an unequal rate. If the transmission of the stimulus actually passes through this muscular bundle, it is evident that localized disease of the bundle may likewise give rise to heart-block.

Erlanger (*Journal of Experimental Medicine*, 1905) repeated the experiments of His and Hering, dividing or compressing the auriculoventricular bundle in the dog. The results of these experiments showed that all forms of heart-block, incomplete and complete, can be obtained by compression of the bundle of His. A comparison of these observations with clinical experiences leads to the conclusion that all the symptoms of Stokes-Adams disease may be explained by lesions which affect the His bundle. Up to the present time no typical case of this disease has been described in which the heart-block was absent; heart-block without and with attacks of syncope representing only two stages of one identical process.

R. J. E. Scott.

HEBOTOMY.—*History.*—In a paper read in Strasburg, in 1844, Lacour mentions that his teacher Stolz advised enlarging the pelvis by sawing through the pubic bone at one side of the symphysis, and demonstrated his method on the dead subject. We then heard nothing further of this operation, now variously called hebotomy, hebotomy, pubetomy, and pubiotomy, until Gigli, in 1894, again proposed it, believing that it would do away with the disadvantages of symphyseotomy while retaining all its advantages. Bonardi was the first who performed the operation as suggested by Gigli on the living. In the last decade the number of pubotomies performed in Europe has been rapidly increasing, due in part to the marked development in technique at the hands of Döderlein and Bumm. In this country but few have been performed, Norris, Montgomery, Bill, and others favoring the procedure; while other obstetricians who admit having done but few or none at all put themselves on record as not in favor of it.

Operation.—The various methods employed divide themselves into three groups: the open by Gigli, the partly subcutaneous by Döderlein, and the strictly subcutaneous by Bumm. Gigli made an oblique incision through the skin over the anterior surface of the pubes, beginning just to the side of the symphysis and running downward and outward to the tuberculum subpubicum, at the outer border of the labium majus. A carrier was then inserted from above downward behind and close to the pubic bone in a line parallel to the skin incision; to this a Gigli saw was attached and drawn through behind the pubes when the latter was divided.

Van der Velde modified the operation by beginning his incision at the superior pubic spine and carrying it obliquely downward and inward until he reached the

labium majus at the level of the vestibulum; he then proceeded as Gigli, dividing the bone parallel to the skin incision. He claimed the obturator foramen would be less likely to be injured by this method.

Döderlein made a small incision along the upper border of the pubes, just internal to the spine, and large enough to enable him to insert one finger behind the bone with which the bladder and retropubic tissue could be pushed away, thus making way for a carrier which he passed vertically from above downward close to the bone along the finger as a guide. After dividing the bone from behind forward, the skin incision was closed. Henkel made a similar skin incision, after which he separated the periosteum from the anterior and posterior surfaces of the bone. With a specially devised instrument he then carried the saw from above, between the posterior surface of the bone and its periosteal covering, down to the lower border of the pubes, where it was grasped by another instrument passed between the anterior surface of the bone and its periosteal covering and drawn up in front of the bone; the latter was then divided from below upward. Henkel claims that as the process of sawing is done under cover of the periosteum there is less chance of injuring the bladder and soft parts.

Bumm makes no incision at all, but uses a sharp-pointed carrier which he inserts 2 cm. from the median line, carrying it from below upward, closely hugging the lower border and posterior surface of the bone, and doing it under guidance of two fingers in the vagina. The carrier comes out 2 cm. from the median line just inside the pubic spine, when the Gigli saw is attached and drawn behind the bone, the latter then being divided from behind forward.

Gigli's and Van der Velde's open operations were not a very great improvement on symphyseotomy, since the great danger in both lies in the large easily infected incision. These operations have practically been abandoned, and to-day the partly and the strictly subcutaneous operations are mostly performed, each having received numerous though unimportant modifications. There is little difference whether the needle is passed from above or below, whether the hebotomy is performed on the side of the fetal occiput or not, the left side being usually selected as it is more convenient for the operator. As regards the relative merits of the Bumm, Döderlein, and Henkel methods, it may be said that in the latter two there is less danger of injuring the bladder with the carrier, and with Henkel's method there is also less danger of injuring it during the process of sawing. These two are therefore the operations of choice when the head is engaged and presses the bladder against the pubes, or when we have reason to suspect a bladder adherent to the pubes as we sometimes find it after pelvic inflammations, or when large arteries are felt pulsating on the posterior surface of the bone. At other times Bumm's simple, easy method is preferable, there being no incision and consequently less chance of sepsis, especially if the genital tract is already infected.

No matter which method is employed, the patient is placed in the lithotomy position and prepared for operation. The bladder must always be emptied, and if a metal catheter can be used it may be possible to tell just to which side the bladder is pushed. The bone should be divided just internal to the pubic spine, but as the latter can often not be felt it is a good rule to divide it two centimeters from the median line. The labium majus should always be pulled well toward the median line and held there so that when released the skin wound will not come directly opposite the bone wound. While passing the carrier the head should be pushed up as much as possible and if the abdomen is pendulous the abdominal wall should also be pulled up, both precautions to avoid injuring the bladder. The arc in which the saw is held should be 120° to 150° as it is liable to break if held at a sharper angle; even so, it is wise to have at least three saws ready for use. When the bone has been divided the amount of separation must be watched,

and any bleeding after sawing should be controlled by pressure from without and within the vagina for a few moments before proceeding. At this stage there are usually no tears since the bones do not separate suddenly. The question now arises whether to deliver at once or to await a spontaneous birth. We should deliver at once if the condition of mother or child demand it, if the patient is a multipara with relaxed soft parts, or if the pains were already poor before the operation. The objections which are advanced against waiting are that it is cruel and that many children have to be delivered with forceps later. As a matter of fact labor is not made more painful by pubotomy, and the forceps operation which is done later is usually only a low one. Tears in the anterior vaginal wall occur no matter which procedure is adopted, but occur less frequently with spontaneous birth so that the latter is preferable in primiparæ with rigid soft parts, provided the child is in good condition and the pains were strong before operation. If it is decided to deliver at once there is again a difference of opinion as to whether labor should be completed by version or forceps; the results so far are equally good with each, the procedure to be adopted depending upon the individual case. Forceps or version, it is well to remember to pull down in the axis of the birth canal and to deliver slowly, for many unnecessary tears in the anterior vaginal wall have been made by pulling forward too soon and too rapidly. If during delivery one suspects a large tear in the anterior vaginal wall it is well to fix a rubber catheter in the urethra, as the latter is sometimes hard to find in trying to repair the rent. Immediately after delivery the bladder should be catheterized and if no blood is obtained the bladder has probably not been injured; on the other hand bloody urine does not necessarily mean a fistula, as it might have been caused by contusion of the tissues; nevertheless if the urine is bloody a permanent catheter should be left in place. After delivery all tears should be repaired and pressure made in the vagina and pubic region with gauze, this acting as a prophylactic of large hæmatomata.

Accidents During Operation.—The hemorrhage is rarely large enough to cause any anxiety. A severe hemorrhage might be caused when there is an extensive anastomosis between the branches of the obturator and epigastric arteries or if the obturator foramen is injured; if the former is present the vessels can be felt pulsating behind the pubes, the Döderlein operation then being preferable; if the latter happens the vessels running through it are injured, an accident which can be avoided by dividing the pubes internal to the tubercle, as the foramen never extends internal to the spine. The usual unavoidable source of hemorrhage is the crus of the corpus cavernosum, this being injured by the carrier, saw, or during the separation of the bones, but the amount is never alarming. The dangers of pubotomy are in proportion to the soft parts, and foremost among the latter is the bladder, it having been injured with every modification of the operation, either directly with the carrier when there is usually no fistula formed, or by the saw, or it may tear with the vagina during delivery, especially if there be old adhesions between it and the vagina. In reading over one hundred cases in literature I found a bladder fistula in ten of them, many of the latter having healed spontaneously. Vaginal tears alone may occur and can usually be easily repaired. In about fifteen per cent. of all pubotomies they are connected with the cut surfaces of the pubes. How to avoid the various accidents has been discussed under operations.

Pelvic Changes Immediately after Operation.—Sellheim, Krömer, and Tandler have demonstrated on the dead person that the amount of room gained is the same as after symphyseotomy and that both sides of the pelvis are equally enlarged. Others hold that the side on which the operation is performed is enlarged a little more than the other. Three centimetres separation of the bone causes the true conjugate to increase one centimetre and the transverse diameter at the brim one and a half centimetres, the outlet being enlarged to a much less

degree. Four centimetres separation of the bones does not affect the sacroiliac synchondrosis, while six centimetres separation does.

After-treatment.—This is simple, the patient is kept on her back for twelve days, an ordinary tight abdominal binder extending halfway down the thighs and a sand bag on either side being considered sufficient support for the pelvis, the old special apparatus and rubber bandages having been abandoned; in fact they are considered detrimental nowadays, the separation of the sawed ends being considered favorable to a permanent pelvic enlargement. On the sixteenth day the bones are as a rule so firmly united that the patient may begin to walk; it is not necessary to wait until movements of the fragments can no longer be detected.

Mode of Healing.—The fact that six months after a pubotomy a firm callus was felt, function was good, and movement of the cut ends was absent (sometimes it is still present) led early observers to believe that the union was always a bony one. While this may be so occasionally, the greater majority of x-ray pictures six months after pubotomy show a light spot between the cut bony ends, from which we must conclude that the callus is not bony and will not become bony, for it is well known that where there is no bony union of a fracture six months after it occurred there will never be one. Palpation, firm union, faultless function thus furnish no criterion for the character of the callus. The x-ray findings were substantiated histologically and chemically by Obergeld and Sellheim, who experimented on animals. They found that microscopically the callus consisted only of connective tissue and cartilage, while the chemical examination showed nine-tenths organic and one-tenth inorganic matter, there being practically no inorganic salts as compared to normal bone, the latter containing two-thirds inorganic matter. They found the consistency of the callus varied with the amount of the inorganic matter, the latter being increased if the cut ends of the bone were rubbed against each other at intervals, or a bandage was occasionally applied around the limb (Bier's hyperæmia). While the latter procedures made the callus harder, they never caused the formation of bone, as osteoblasts were always absent. Feeding of phosphorus and lime had no effect on the callus.

The Permanent Enlargement of the Pelvis and Future Pregnancies.—As the x-ray pictures show the cut bony ends still separated, though united by a firm non-bony band at the end of six months, the true conjugate must remain enlarged, and various statistics bear this out, among them Kannengiesser's of eighteen cases, with enlargement of from one-half to one and a half centimetres. This permanent enlargement of the true conjugate does not, however, necessarily mean that the inlet of the pelvis is permanently enlarged, for the callus may protrude far enough backward to become an obstruction at a future delivery. The latter occurrence is, however, the exception, the majority of the pelvis showing no such projection; their inlet, therefore, being permanently enlarged. In ten successive cases of Preller there was no such posterior projection of the callus. Even though a majority of the pelvic inlets are permanently enlarged, it is by no means certain that all future deliveries will be non-operative, for the enlargement may not be sufficient, but some will certainly be spontaneous. Baisch reports seven patients who had had a hebotomy performed and who became pregnant again; four were delivered spontaneously and on three a second pubotomy was performed. In eight of Kannengiesser's patients three of the succeeding deliveries were spontaneous, in three labor was induced prematurely, one was pubotomized, and in one a cesarean section was performed.

Prognosis.—The results for the child have not been so good as for the mother. Out of 226 births after pubotomy all but 15 children were delivered in good condition, a mortality of not quite 7 per cent. The deaths were usually due to pressure from forceps, or occurred after version when the head could not be delivered rapidly enough.

The maternal mortality of different operators varies from 2 to 6 per cent. I have collected 366 cases and found a mortality of 3.2 per cent., a small number when we consider the many errors which are sure to make the results of a young operation worse than they should be. The deaths usually occurred in patients who had been previously infected, sepsis being the cause. Even if the histories are reliable we cannot lose sight of the fact that the injuries of the soft parts during operation increase the liability of sepsis. One death was due to chloroform, one to an uncontrollable hemorrhage (von Rosthorn's patient), and several to pulmonary embolism, the latter following thrombophlebitis, which occurs more frequently after a pubotomy than after normal deliveries.

Morbidity.—Fifty per cent. of the patients experience slight annoyances, usually due to a slight infection of the injured soft parts, or to a hematoma which usually disappears after three weeks, or to thrombophlebitis. Outside of being more likely to get a prolapse of the anterior vaginal wall the ultimate results are perfect, as the patient's gait and ability to work are never affected.

Indications and Comparisons with Other Operations.—Various figures have been mentioned as the lowest grade of contraction in which pubotomy may be performed. To fix a limit is impracticable, as the size and compressibility of the head must be considered. This much may, however, be said: whenever the operation is performed on a flat pelvis the true conjugate must be at least 6.75 cm., when on a just-minor pelvis at least 7.5 cm., furthermore the child must be alive. These conditions fulfilled, the operation has been advocated for the following conditions:

1. Mother not infected and when from the beginning the disproportion in size between head and pelvis makes it impossible to hope that the head can pass through the pelvic brim.
2. Similar conditions to No. 1, except that mother is infected or there is a suspicion of infection on account of examinations under doubtful asepsis.
3. Mother not infected, some doubt as to relation in size between head and pelvis, and when in spite of good contractions the head still moves freely above the brim, especially in a multipara who had a previous still-birth.
4. Similar conditions to No. 3 except that mother is infected or there is a suspicion of infection on account of examinations under doubtful asepsis.
5. Impacted face presentation, chin posterior after attempted rotation with forceps without success.
6. Head engaged, no headway, time for version passed, after an attempted delivery with forceps without success.

From the above it at once becomes clear that pubotomy is occasionally a competitor of symphyseotomy, perforation of the living child, induction of premature labor, cesarean section, version, and high forceps. Perforation of the living child is rarely if ever indicated, and symphyseotomy has been abandoned in this country and by most clinicians in Europe on account of its many disadvantages, so that we may at once eliminate these two operations from the above list. As regards induction of premature labor it is but seldom a competitor, as the majority of the patients usually do not come under our observation until in labor; if, however, we see the woman early the question of choosing between premature labor and pubotomy arises. The mortality of the mothers is less in the former than in the latter, but that of the infants is only seven per cent. as against twenty per cent. after prematurely induced labor, so that there is but little preference when we have the opportunity to choose; in fact the combination of the two methods has been suggested by some, in order that the head will not be too large and cause too great a separation of the bones and that the induction will not be too early with its consequent dangers for the child. In the greater number of cases the time favorable to the induction of premature labor has passed and cesarean section, version, and high forceps remain as the only competitors of pubotomy.

Under the above heading indication No. 1 our choice can lie only between cesarean section and pubotomy. Under these conditions the results of cesarean section in the hospitals in this country have been excellent. A. B. Davis at the New York Lying-in Hospital lost only 4 patients out of a total of 38, all these having been previously infected, so that the mortality is *nil* in cesarean section as regards mothers in clean cases, with the additional advantage that the operation is free from hæmatomata and injuries of the soft parts and that the patient is able to attend to her work at an earlier date. Only 2 children (in the clean cases) were not alive when the mothers were discharged. We thus see that here cesarean section is preferable to pubotomy, unless the surroundings are not adapted for cesarean section or the operation is refused, or when there is a prolapsed pulsating cord in which case the preparations for the cesarean operation might take too long.

Under indication No. 2, we can again choose only between cesarean section and pubotomy. Here the generative tract is infected, under which circumstances a cesarean operation is dangerous as the peritoneal cavity is opened and general peritonitis easily results. Davis lost 4 out of 6 infected cases, a much higher mortality than in the infected cases in which a pubotomy was done. Pubotomy is therefore preferable in these cases; the chances for the child are the same in both procedures.

Under indication No. 3 it is more difficult to decide; personally, I believe that, in a hospital, cesarean section would give the best results, but if we cannot do it we must decide between pubotomy, version, and high forceps. If high forceps requires too much force, pubotomy is to be preferred, as more children will be discharged alive, the chances for the mother being about equal. If version is decided upon and there seems to be any doubt as to the head passing the brim, it is well to pass the carrier and lay the saw in place before doing the version, so that the bone can be sawed through quickly if there is any difficulty in extracting the head.

Under indication No. 4 the same remarks apply as under No. 3 except that cesarean section is excluded on account of the existing infection.

Under indications Nos. 5 and 6, pubotomy only is indicated.

That pubotomy can be easily performed in private practice is evident from the fact that many have been successfully performed in the out-patient departments of German clinics; it is also eminently more suitable for the general practitioner than cesarean section.

C. Frederic Jellinghaus.

HELMITOL is hexamethylenetetramine anhydromethylene citrate, $C_7H_{10}O_7 \cdot (CH_2)_6N_4$. It occurs in colorless crystals, soluble in ten parts of water, almost insoluble in alcohol and ether. It is slowly decomposed in dilute acid solutions, readily in alkaline solutions with the liberation of formaldehyde. Solutions have an acid taste and reaction.

Helmitol is a urinary antiseptic in much the same manner as is hexamethylenamine. It is equally efficient in acid or alkaline urine. Used in chronic urethritis, cystitis, and chronic affections of the bladder, it arrests the alkaline fermentation of the urine, relieves tenesmus, and is said to be especially useful in pyelitis and as a urinary disinfectant following typhoid fever. Dose: 10-15 grains (0.6-1.0).

John W. Wainright.

HEMLOCK, POISONING BY.—The water hemlock (*Conium maculatum*) is a small herb, belonging to the natural order *Umbelliferae*. It is indigenous in Europe, but has established itself in other countries. It is regarded as the poison used by the ancient Athenians in putting criminals to death, and has become famous in consequence of its use in the case of Socrates.

The poisonous properties exhibited by several parts of the plant, especially the fruit, are due to several alkaloids, of which coniine is the most important. Its formula is $C_8H_{17}N$. It is a colorless liquid, specific grav-

ity about 0.880, not very soluble in water. It boils at a temperature considerably above that of water, and has a distinct rotary action on polarized light. Its odor is strong and disagreeable.

Cases of hemlock poisoning have been mostly accidental, parts of the plant having been mistaken for edible herbs, such as parsley. The following are the most marked symptoms: Headache, vertigo, dilated pupils, a prickling sensation in the extremities, with gradually developing paralysis. This latter usually begins in the legs. The paralytic condition extends to the muscles of the trunk and neck, speech and deglutition become imperfect, and finally asphyxiation may occur by failure of the respiratory muscles. The mind is not much impaired until the latest stages of the case. Convulsions may occur at an advanced stage. A case may last several hours, but is likely to be much more rapid in its progress, death sometimes occurring in a few minutes. The poisonous dose is small, but cannot be accurately fixed from the data at hand.

Tannin and animal charcoal have some antidotal value, but the thorough washing out of the stomach will be found to be of most advantage and should be instituted as soon as possible. Artificial respiration may be required in the advanced stages of the case. The marked paralytic condition suggests the cautious use of strychnine in very small doses hypodermically.

The detection of the characteristic alkaloid is a difficult matter, but its peculiar odor will be of value. More important, from a practical medical point of view, is the recognition of parts of the plant. These should be carefully examined, and compared with authentic specimens, or mistakes will be made, for species of *Umbelliferae* are often difficult to differentiate. The post-mortem appearances are not characteristic.

Henry Leffmann.

HICCUGH (singultus) is caused by a spasmodic contraction of the diaphragm, with sudden closure of the glottis. The condition may be: (a) *Irritative*, as when the spasm is excited by swallowing hot or dry food, disease of the lower extremity of the œsophagus, gastric or intestinal indigestion; (b) *inflammatory*, occurring in gastritis, peritonitis, appendicitis, hernia, internal strangulation, or typhoid fever; (c) *specific*, in which the condition accompanies cancer of the stomach, mediastinal tumor, gout, diabetes, nephritis, or other constitutional disease; (d) *reflex* or *neurotic*, occurring in hysteria, cerebral tumor, epilepsy, emotional disturbance, shock, or from peripheral irritation. The attacks vary in duration from a few hours to several weeks or months.

The prognosis is seldom unfavorable except when the spasm complicates some serious organic disease.

TREATMENT.—In the less severe cases many of the popular remedies are effective, as holding the breath, taking a drink of cold water, swallowing ice, salt, vinegar, lemon-juice, or strong brandy, a sudden fright, or the induction of sneezing. Prolonged, firm pressure in the epigastrium, a tight bandage around the lower thorax, massage of the abdomen, faradization, an emetic, passing the œsophageal sound, or lavage of the stomach, will relieve some of the more severe cases. The cold pack is often promptly curative. Of internal remedies there are many, but they must be tried in succession in the worst cases, and none is infallible. Of these, the best are: Cocaine, gr. $\frac{1}{4}$ (0.01), spirit of chloroform, 3 ss. (1.8), codeine, gr. ss. (0.03), asafetida, and the bromides. Morphine may be employed hypodermically in the worst cases, but its effect is transitory. Pilocarpine, nitroglycerin, apomorphine, and inhalations of chloroform or amyl nitrite may be curative. Pressure on the lower part of the thorax or over the phrenic nerve, and galvanism may be tried.

James M. French.

HUNYADI JANOS SPRING, AUSTRIA.—A mineral spring at Ofen, Hungary, a part of Budapest. The active ingredients are the sulphates of sodium and magnesium. The following table shows the proportions in which they occur in the various Hungarian waters.

ONE LITRE OF WATER CONTAINS:

	Sodium sulphate. Grams.	Magnesium sulphate. Grams.
Hunyadi Janos	22.55	22.35
Franz-Josef	23.18	24.78
Apenta	15.40	24.40
Puellna	9.59	10.85
Friedrichshall	6.05	5.15
Kissingen Bitterquelle....	5.80	5.00

The following is an analysis of the Hunyadi Janos water by Professor Bunsen. One pint contains: Sodium carbonate, gr. 13.20; ferrous (oxide) carbonate, gr. 0.08; calcium carbonate, gr. 6.04; strontium carbonate, gr. 0.19; sodium chloride, gr. 11.54; potassium sulphate, gr. 1.67; sodium sulphate, gr. 128.97; magnesium sulphate, gr. 137.98; silicious earth, gr. 0.09. Total, 299.76 grains. Free and partly combined carbonic acid, 8.06 cubic inches.

Other well-known waters of like character are those of the Rubinat Condal, Rubinat Serre, and Rubinat Llorach Springs in Spain.

The taste of these waters is disagreeably bitter, much like a solution of "Epsom salts," although it is said to be somewhat modified by the presence of free carbonic acid and the other salts; at best, however, they are not a pleasant drink.

These sulphated bitter waters are much employed either as an occasional aperient, or in habitual constipation and in dyspepsia accompanied by constipation. They are also a serviceable laxative in small doses in pregnancy, arteriosclerosis, cardiac disease, and other morbid conditions in which an unstimulating laxative is desired. In large doses they are indicated where a rapid, full evacuation of the bowels is the end in view. In brief, in all the innumerable conditions in which a "dose of salts" is indicated, these bitter waters, which are practically a solution of salts, can be used. The usual dose of the strong bitter waters is from a half to one wineglassful taken on an empty stomach. In emergency cases a larger dose can be taken—from three-quarters to one tumblerful.

Edward O. Otis.

HYPERÆMIA, ARTIFICIAL, AS A THERAPEUTIC AGENT.

—During recent years August Bier has developed a method of treating a great variety of diseases by the production of localized hyperæmia. The exact position of this therapy cannot be defined at the present time, but in view of the fact that it has proven very useful and effective in the hands of a great many physicians and surgeons, it seems destined to play an important part in the treatment of many diseases. As with most new agents, hyperæmia produced by the technique elaborated by Bier has been extolled by some in a most exaggerated manner and it will undoubtedly require years of patient study and observation before the proper place is allotted to this useful therapeutic agent. Exaggeration and overenthusiasm work injury and are sure to delay the general adoption of Bier's methods. Indiscriminate application of this therapeutic agent also works injuriously in the same way. An attitude of scientific reserve and careful investigation should be pursued, and finally all will clearly see the advantages and the disadvantages as well as the limitations of artificially produced hyperæmia. At the present time one can already say with considerable definiteness what this agent can effect in a great variety of pathological conditions, but in the realm of severe acute inflammatory diseases a scientific scepticism must be maintained until the *post hoc* developments are absolutely and irrefutably proven to be *propter hoc*.

"Every working, functioning organ is hyperæmic while doing its work." "All growth and regeneration are accompanied by local hyperæmia, which is all the more marked the more active and energetic the growth." "All body reactions to foreign materials, in the broadest sense, are accompanied by hyperæmia" (Bier). Hyperæmia is therefore the most common agent that

Nature avails herself of, in both normal and diseased conditions. In following the example of Nature, Bier has developed a new therapeutic field as well as a more modern conception of many pathological conditions.

During recent years the medical world has gradually faced about on the question of inflammation so that nowadays this process is recognized as something useful and reparative. Bier has emphasized this more than any other writer, and upon this he has based much of his work with hyperæmia. The practical application of the pathologist's views above mentioned we owe to Bier, who says, "Away with antiphlogistic measures, and let us assist Nature and increase the body's response, i.e., the inflammation."

In producing localized hyperæmia one must keep the two types of hyperæmia separate, as their therapeutic usefulness is very different. *Active or arterial hyperæmia* is regularly seen after removal of an Esmarch bandage which has been used to produce ischæmia. The part rapidly becomes bright red after removing the bandage. The same type is produced by active use of our muscles, by massage, and by the use of electricity. Chemical and thermic irritants produce this arterial hyperæmia very readily, and the latter is particularly useful as a therapeutic means of producing this type of hyperæmia.

Opposed to this is the more subtle type of hyperæmia, the *passive or venous*. This is most readily produced by constriction of the return circulation, which naturally produces a venous engorgement of the distal parts. On removing the constricting bandage a more or less marked active or arterial hyperæmia sets in and takes the place of the previous venous hyperæmia. Another practical method of producing this hyperæmia is by the use of dry cups. Here, as in the constriction hyperæmia, the venous hyperæmia may not be the only type produced. Just as arterial follows venous hyperæmia when a constricting bandage is used, so under the cups there may be a combination of the two types of hyperæmia. This point is still unsettled.

It is of great interest to note that Bier originally began to use artificial localized hyperæmia in the treatment of surgical tuberculosis in the early nineties of the last century. His attention was drawn to the possibilities of this treatment by the following observations, then generally accepted:

1. That the lungs were regularly the seat of tuberculosis, if the blood supply was deficient, e.g., in pulmonary stenosis the patients with great regularity died of tuberculosis of the lungs.

2. That, in acquired heart disease leading to pulmonary congestion, active tuberculosis rarely was found in the lungs. If venous congestion effected so much in the pulmonary circuit, Bier reasoned that a similar condition in the systemic circulation would probably lead to an equally beneficial result. This stimulated him to apply the constricting bandage in tuberculosis of bones and of joints; this marks the origin of his work with venous hyperæmia. It is evident that the above reasoning is not faultless, as it is scarcely probable that the blood in the pulmonary circuit is venous in character, except in the larger vessels close to the heart. In the capillaries the blood rapidly becomes arterialized, so that the diseased areas are bathed in arterial rather than venous blood. Despite the fact that Bier's superstructure was thus erected on a faulty deduction, it will be evident in the succeeding pages that it promises much as a therapeutic agent.

In general Bier ascribed the following activities to hyperæmia: (a) It diminishes pain; (b) it is bactericidal and works as a diluent; (c) it hastens resorption and assists in absorption; (d) it aids nutrition; (e) it acts mechanically in effecting good drainage.

(a) There is no doubt that hyperæmia has a marked effect on pain, though for reasons still unclear it occasionally fails to diminish it. It is thought that the œdema resulting from the production of artificial hyperæmia works much as Schleich's infiltration anæ-

thetia. At the same time the œdema dilutes the concentrated and irritating exudates which surround the nerve filaments. Bier has called attention to the fact that in periostitis of the jaw, the pain ceases as soon as the cheek swells, and fractures in an extremity cause no pain when the limb becomes swollen. In these observations, that as soon as marked swelling develops, pain diminishes, I do not believe all surgeons will agree. Since my attention was first drawn to this contention some years ago, I have noted the point carefully and failed to convince myself of its accuracy. Still there is no denying the fact that a properly applied bandage producing constriction hyperæmia will very frequently diminish pain. Both arterial and venous hyperæmia act in this way.

(b) Hyperæmia increases the local bactericidal powers and dilutes localized poisons. The latter action is the more readily understood. It is well known that what would be a fatal dose of a poison in a concentrated solution, can be given in a much diluted solution without a fatal result. The œdema engendered by the constriction of a limb dilutes the toxins in just this way, while at the same time the same fluids are acting as bactericidal solutions. Colley's experiments go to show that the œdema produced in an infected limb is much more bactericidal than that produced in the same way in a non-infected limb. This property of the serum is due to a great variety of factors. Hamburger has called attention to the fact that œdema fluid is more bactericidal than the circulating blood plasma, and he ascribes this in part to the increased CO_2 and alkali content. It has also been shown that hyperæmia produces a local increase in leucocytes, and Heile's work demonstrating an increased excretion of purin bases can be best explained by a rapid breaking down of large numbers of leucocytes. It has also been shown that the use of the constricting bandage raises the local opsonic index. There can be no doubt as to this bactericidal effect of constriction hyperæmia, though whether all bacteria are affected equally is doubtful. Clinical experience bears out the experimental work done up to date. How much of the bactericidal and of the diluent effects is produced by the incomplete stasis in the veins and how much by the same condition in the lymph circulation, future investigation will perhaps demonstrate. In the past the effect of constriction in the lymph circulation, which surely is affected first of all after the bandage is applied, has been almost entirely ignored. My clinical experience forces me to consider this an important element, especially in the production of the local œdema and in the marshalling of the forces that develop in this bactericidal fluid. Venous hyperæmia is particularly useful in combating the bacterial invasions and is therefore used instead of arterial hyperæmia in localized infectious processes.

(c) The clinical fact that hyperæmia aids in the absorption of fluids and soluble matter, whether these be within the body or upon its mucous surfaces, was accepted long ago. Klapp has shown by experiment, very recently, that arterial hyperæmia hastens quite markedly the absorption of injected lactose. On the other hand, venous hyperæmia, so long as the bandage remains in place, diminishes local absorption. On removal of the bandage, absorption increases markedly. Bier doubts whether this secondary effect takes place if the constricting bandage is in place for many hours, and consequently employs massage to aid absorption.

Though venous hyperæmia is not capable of accelerating absorption of fluids and of soluble substances, still it does seem to have a distinct absorptive action on certain pathological lesions. Bier refers to cases in which this form of hyperæmia has led to the absorption of thickenings in and about joints, of thickenings in tendons, of keloids, etc. In this particular realm it is wise to reserve judgment until better evidence is at hand. Though we cannot deny that in acute or chronic suppurative processes all sorts of tissues melt away as a result of the disease, still in Bier's therapy we do not

reproduce the condition of acute or of chronic inflammation, but only one symptom of this process. Dissolution of tissues in inflammatory conditions is probably due to some obscure activity, perhaps fermentative or autolytic, and as yet the proof is lacking that simple constriction of a limb leads to these activities.

Despite these theoretical conditions one cannot deny that stiff joints improve under arterial and venous hyperæmia. The explanation of the process is by no means simple.

(d) Another activity or property ascribed to hyperæmia is the nutritional. Bier bases this claim upon a great variety of clinical data which are best read in his monograph. Regeneration of tissue is most active in inflamed areas, in fact it is usually excessive, and, as Bier believes, here venous hyperæmia dominates the field. In the growth of the foetus a well-marked venous engorgement (*hyperæmia*) prevails in the placental channels. In patients suffering from femoral vein thrombosis one frequently sees well-marked thickening of the extremity which possibly is in part due to a local hypertrophy resulting from venous obstruction. That this thickening is not due to deep œdema alone, I feel sure from a case of bilateral femoral thrombosis that I have watched for a matter of a dozen years since the thrombosis developed. The observation that the epidermis becomes thickened and hairs increase in number near chronic ulcers points to a distinct nutritional effect. Arterial hyperæmia also exerts a nutritional effect in the epidermis, according to Bier. On the other hand, chronic congestion of the viscera does not lead to increase of the connective tissue or hyperplasia of the parenchyma with any regularity. The latter result is unknown, whereas increase of the connective-tissue stroma is a moderately frequent result. While hyperæmia appears to have no nutritional effect on the viscera, in the sense of leading to excessive growth and increased size of the parenchyma, Bier claims that it has some such effect on bones and connective tissue as well as upon the epidermis. Most of the data which Bier has gathered to prop this contention are scarcely sufficiently cogent to settle this particular point as to the nutritional effects of venous hyperæmia, and until we obtain more data based on more modern and accurate work than that referred to by Bier, here again it will be well to reserve judgment. On the other hand, arterial hyperæmia probably does make for a more healthy nutrition. For there can be no doubt that improvement in the peripheral circulation will frequently lead to a healing of ulcers or abort a threatened gangrene in diabetics or in old arteriosclerotic patients.

Until exact experimental evidence is produced showing that a constriction bandage will actually and regularly lead to increase in growth of the tissues in a limb, and until patients with chronic localized cyanosis show some changes due to forced nutrition, it is absolutely necessary to exercise all our scientific scepticism as to the nutritional value of venous hyperæmia.

(e) To any one who has employed either constriction hyperæmia or suction hyperæmia it is surely evident that a mechanical irrigation of the diseased areas must regularly occur. In using the suction cup over an incised abscess, the most perfect and complete drainage is induced. The pus and débris are rapidly withdrawn and, after the cavity has been drained of these, bloody serum pours into the cup. The latter acts as an antiseptic solution and washes out every nook and corner of the infected cavity. In addition to this distinctly mechanical effect the adjacent tissues under the cup become œdematous and hyperæmic. On the other hand, the constriction bandage above an inflammatory area which has been incised leads to an identical result. It produces an œdema, and this fluid is poured out copiously through the incision, thus thoroughly irrigating the diseased tissues from within. This constant flow from within outward washes out all the pus and débris and thoroughly disinfects the involved areas. A more ideal method of irrigation is inconceivable, and though

I would not attribute the good results of Bier's method to this factor alone, as some are inclined to do, still I do feel confident that this peculiar activity is one of the most important and beneficent of those exerted by artificially induced venous hyperæmia. That it would be

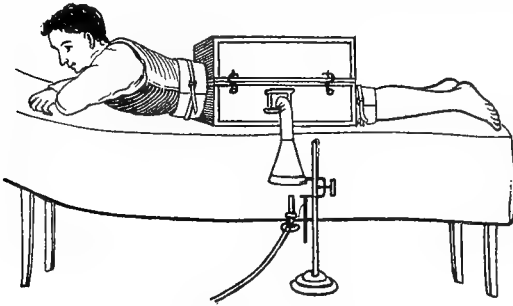


FIG. 5172.—Hot Chamber for Both Hips.

an exaggeration to say that this is the sole beneficent activity of hyperæmia will be self-evident to any one who has treated non-incised cases and effected a cure without making use of these mechanical principles that make for perfect drainage.

This most evident activity Bier has not emphasized as much as it deserves, which probably explains the zeal with which some have seized upon this as the important process underlying artificially induced venous hyperæmia.

Technique of Application.—Arterial hyperæmia is produced by the use of heat, in the form either of hot air or of hot applications. As both methods are well known to the profession, this phase of the subject can be treated briefly. Bier has employed the skill of Eschbaum, a local instrument maker, to perfect a great variety of hot-air boxes which are so modelled that they fit on most of the surfaces of the body. (See Figs. 5172 and 5173.) Large boxes with vertical slits have been constructed to permit of hot-air applications to the spinal column. Other boxes have been made so as to encompass the pelvis and both hip joints. Smaller boxes are on the

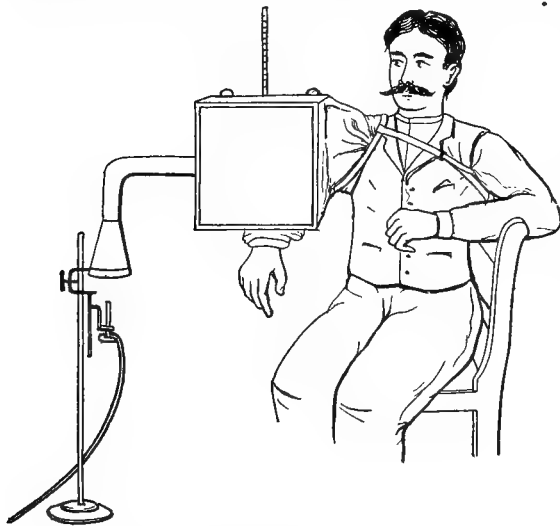


FIG. 5173.—Hot Chamber for the Shoulder.

market for applications to the extremities. The openings in these boxes are lined with heavy material which prevents undue escape of the heated air. A similar result can be obtained by surrounding the parts of the body that lie in the openings of the box with heavy felt. The air is heated before entering the box by means of

a gas or alcohol flame which is placed below the funnel tube that connects with the interior of the box. A thermometer, so placed within the box that it can be read without opening the same, will aid in controlling the temperature to which the exposed part is subjected. Marked active hyperæmia develops between 80°–120° C. (176°–248° F.). Though many prefer to surround the exposed part with cotton or flannel, Bier, despite the fact that he admits that this diminishes the danger of burning the patient, has given it up. He thinks these enveloping materials become moist and thus prevent a marked arterial hyperæmia. It is wise, however, to place pieces of flannel between opposed skin surfaces so that no burns occur.

To obtain a more localized action and where these hot-air boxes cannot be applied, *e.g.*, the face, a great variety of hot-air douches are used. Bier employs for this purpose a simple machine (Fig. 5174) which is so protected that it can be moved about, permitting the operator or patient to throw the stream of hot air in different directions. This instrument resembles the chimney of his hot-air boxes and is well shown in the accom-

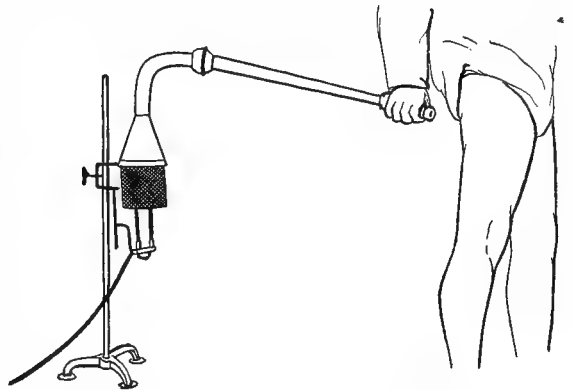


FIG. 5174.—Hot-air Douche Applied for Sciatica.

panying figures together with several of his hot-air boxes.

Much difference of opinion as to the duration of each treatment prevails. In some cases short applications (of ten minutes) are indicated, in others longer applications up to an hour or an hour and a quarter might be more useful. In general short treatments are used where there is danger of gangrene or where many joints are treated each day. Longer treatments are used in chronic conditions, such as rheumatic joints.

The use of hot fomentations is so general that it need not be entered into here. They produce hyperæmia just as hot air does and by virtue of this action accomplish much that is beneficial.

To produce venous hyperæmia, for most cases a less expensive armamentarium will suffice. The development of part of this field is due to the ingenuity of Klapp, who deserved great credit for his important work along the lines of suction hyperæmia.

Suction Hyperæmia is induced by the aid of a variety of glass cups (Figs. 5175–5182) which are of various shapes and sizes, permitting their ready application to different surfaces. The smaller cups are fitted with hand bulbs, whereas the larger cups require a hand pump to produce the necessary rarefaction within the cup. In the treatment of most cases the smaller cups are perfectly adequate, but in the treatment of more extensive inflammatory foci very large cups are required (Fig. 5182). Especially large cups are made for treatment of inflammatory conditions of the breast and hand. In cases of stiff joints, where the whole arm or knee is exposed to this type of hyperæmia for orthopedic exercises, expensive apparatus is necessary (Figs. 5183–5185). All these cups are made by Eschbaum and are now to be had in New York City.

As the suction in inflammatory cases draws out pus, bacteria, etc., the cups are very regularly contaminated. Cups such as shown in Figs. 5176 to 5181 are designed to prevent the entrance of infectious materials into the

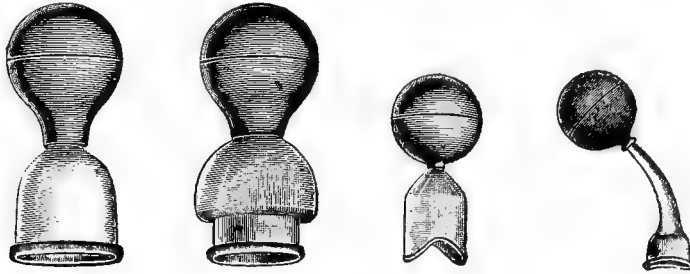


FIG. 5175.

rubber ball or rubber tubing. The cups must be kept clean by boiling or by use of antiseptic solutions. In using the very large vacuum glasses for orthopedic purposes naturally no such measures are necessary, as these cups are not contaminated. They are not employed in the treatment of inflammatory diseases, but are apparently of use in stretching stiffened joints and adherent tendons by virtue of the pressure exerted by the atmosphere. This is most clearly seen in Fig. 5185.

On the other hand, venous hyperæmia produced by constriction requires very little in the way of appliances.

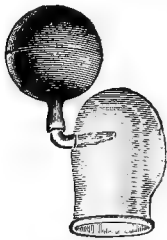


FIG. 5176.

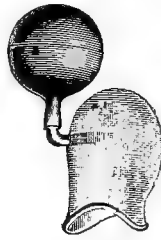


FIG. 5177.

A thin rubber bandage suffices for all extremity cases except the most proximal parts. In the hip there is no way of producing this type of hyperæmia; whereas in the shoulder joint, as shown in Fig. 5187, a rubber tube must be employed. To produce hyperæmia distal to the neck elastic webbing is used. These neck bands are so arranged with hooks and eyes that their tension can be readily regulated. It is evident that this useful type of hyperæmia can be employed without any great expense, and for the benefit of those who wish to try this new therapeutic agent I can say with perfect honesty

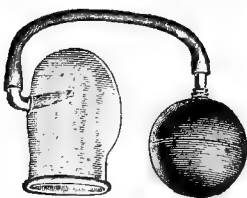


FIG. 5178.

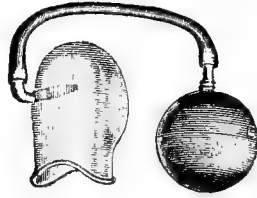


FIG. 5179.

that they need not purchase at once a great variety of suction cups; a few sizes and shapes, e.g., such as are represented by Figs. 5175, 5180, 5182, and a Martin's rubber bandage, two and one-half inches in width, will suffice to begin.

Technique of Suction Hyperæmia.—After making a small incision provided pus is present (and gently squeeze-

ing this out*) the cup is applied. Two cardinal rules must be followed. The application of the cup must be painless and intermittent. If the suction is extreme it causes pain and damages the tissues. In acute inflam-

matory conditions the suction should regularly be mild, whereas in more chronic conditions, especially over sinuses, one may exert considerable suction. Pain on the part of the patient is an indication of faulty application. Subcutaneous hemorrhages about the diseased focus are another sign of faulty technique. Just as important as the observation of painless application is the intermittent suction. Suction should not be continuous. There should be intermissions every four or five minutes, and then suction again for four or five minutes after a two- to three-minute pause. This routine is kept up for forty to forty-five minutes, and the

whole constitutes one treatment. Such a treatment may be given once or twice a day. It is frequently advisable to grease the edge of the cup with sterile vaseline so that the cup takes better hold on the skin. The cups that are used for the fingers (Fig. 5181) or for the hands are supplied with a rubber cuff which must be made to enclose the more distal part snugly to permit of the production of a rarefaction of the air in the cup. While the cup is drawing on the exposed part, the latter becomes hyperæmic and swells. It projects into the glass. The circulation of the exposed tissues becomes sluggish. The incised focus of the sinus discharges more or less freely. On removing the cup, which is done gently by squeezing the rubber bulb together or by allowing air in

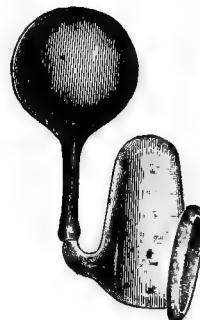


FIG. 5180.



FIG. 5181.

by the stopcock, the exposed part has an opportunity to regain a more normal circulation. Fresh blood pours into it and some of the artificial cedema disappears. After a short pause suction is again applied, and so on till the treatment is concluded.

To make the technique absolutely clear I will briefly narrate three cases that were treated by this suction method. These will illustrate more graphically just how to use the cups and at the same time show some of the advantages of suction hyperæmia.

CASE I.—F., 35 years. For one week the patient has had a painful, red swelling on outer side of forearm. This has gradually grown in size. When I first saw it it measured about one and one-half inches in diameter and fluctuated. Diagnosis: Abscess. After selecting a properly shaped cup which would encompass the whole

* Bier advises pressing out the pus, which is not necessary either in suction or in constriction hyperæmia, as both make for excellent drainage and painless evacuation of the inflamed foci.

area of inflammation, I made, under local anæsthesia, a one-half-inch incision over the middle of the abscess and at once applied moderate suction hyperæmia, without producing any pain. Large quantities of pus and of



FIG. 5182.

blood discharged into the cup, and after four or five minutes' suction the cup was removed. After two or three minutes' rest the cleaned cup was reapplied as at first and more pus and blood discharged. The adjacent skin became deep red in color and the whole area became turgid with congested blood. After four or five minutes' suction another period of rest and then suction

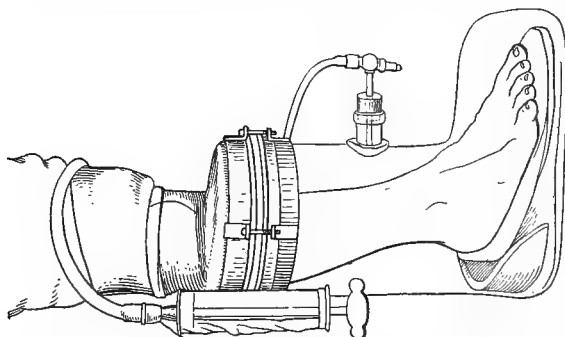


FIG. 5183.—Orthopedic Apparatus for Producing Hyperæmia and Forced Dorsal Flexion in Ankle Joint.

again. After doing this for forty to forty-five minutes, suction no longer withdrew pus and the small incision was choked with blood clot. The arm was then dressed with a wet dressing, *no drain being used*. The patient declared that after all the manipulation her arm felt much better and almost all the pain had left. As the patient was sufficiently intelligent to make proper use

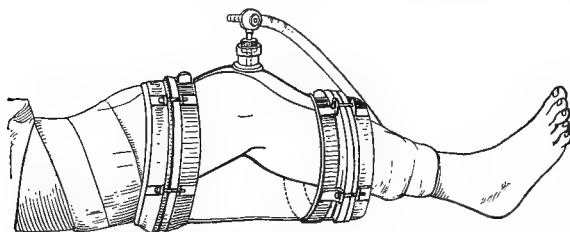


FIG. 5184.—Orthopedic Apparatus for Producing Hyperæmia and Forced Flexion of Knee Joint.

of the cup, I gave her the cleaned cup to apply as I had done. She employed it that evening, and returned to me next day for the third treatment, which was scarcely required. Almost all signs of inflammation had disappeared. There was very little tenderness or redness.

The swelling had gone down. There was no pus. For safety's sake I gave her one more treatment and applied a light wet dressing. In this case, within thirty-six hours after the incision, the inflammatory focus had practically disappeared without causing the patient any

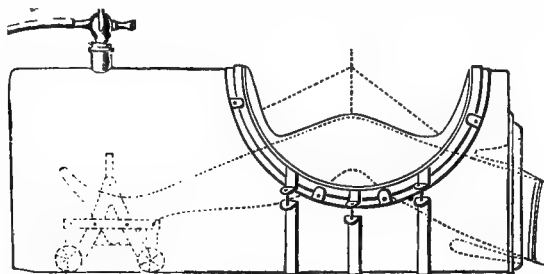


FIG. 5185.—Orthopedic Apparatus for Hyperæmization and Stretching of Knee Joint.

of the usual pain incidental to the older methods of treatment by broad incision and packing.*

CASE II.—F., 20 years. Three days previous had been manicured. Since then painful, red swelling about nail, especially over the matrix. Since this morning there was a slight discharge of pus from below the cuticle. Diagnosis: Paronychia. As the focus was discharging, I immediately began to employ suction hyperæmia without incising, using the cup represented in Fig. 5181. The same technique was employed as in the previous case. Some pus and bloody serum discharged. The finger became red with the slightest tinge of blue. The next day and the day following I used the cup again, bandaging the finger with a wet dressing between treatments, and by that time the infection was controlled and the patient was discharged.†

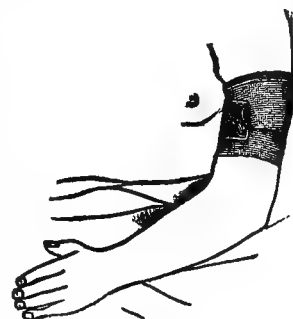


FIG. 5186.

CASE III.—M., 15 years. Has sinus over head of tibia following operation for supposed tuberculosis of the bone. The sinus, which was one and one-half inches long, did not lead to bare bone. Diagnosis: Post-operative sinus. After greasing the lips of the small sinus cup with sterile vaseline to assist in gaining proper apposition, the treatment as above outlined was carried out. Suction was applied. Serum and blood escaped into the cup and the granulations became turgid. After one such treatment the sinus was closed so that when seen two days later no further suction therapy was necessary.

In the use of the very large cups for orthopedic purposes Bier gives less explicit rules. The part to be exercised or stretched is first made hyperæmic and after this is thoroughly done the air is rarefied even more, the degree of rarefaction required being tested on one's own

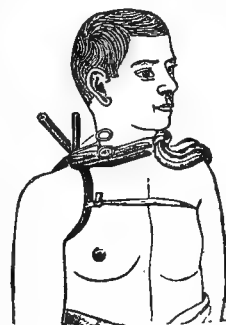


FIG. 5187.

*Other illustrative cases similar to this can be found in my paper in the Medical Record, August 25th, 1906.

†In some hand cases large hand cups are very useful in producing hyperæmia.

arm, or other part first, or by close scrutiny of the patient's limb. The atmospheric pressure forces the limb into the vacuum; as, for instance, in the case of a plantar-flexed foot the pressure would force the extremity against the glass base and thus stretch the involved parts, gradually extending the foot further and further, until pain becomes too severe or complete extension has been obtained. The same process of stretching is carried out in this way in the knee, wrist, elbow, and finger joints with the proper appliance. Special instruments with spiral groove and fitted with a hand piece to develop supination and pronation are warmly recommended by Bier.

Technique of Constriction Hyperæmia.—Though the constricting bandage has been used a great deal, the exact application of it is still difficult. Henle tried to simplify the technique by using a rubber tube connected with a manometer. This can be applied to produce the same pressure each time after one has determined the pressure one desires in the particular case. Bier finds this useful in difficult cases. As a rule, a thin rubber Martin's bandage suffices. This is applied over a piece of gauze or directly to the skin, one fold of the bandage overlapping the other. The end of the bandage is fixed with a safety pin. The exact tension of the bandage is best studied on one's own arm. Such a preliminary study prevents many awkward experiences for the physician and many painful moments for the patient.

Though Bier does not specify accurately that these constricting bandages are applied differently in chronic and in acute conditions, still his reference to the treatment of tuberculosis, and my own extensive experience with his methods, have led me to use firm constriction in the more chronic cases and mild constriction in acute cases.

The technique is very similar, though much more difficult in the acute cases. The bandage is wrapped about the limb proximal to the diseased part, as described above, and the tension is regulated by the subjective and objective symptoms. In chronic cases the bandage is applied firmly until the veins stand out and the part distal to the constriction becomes reddish blue in color. Such an application should not produce a mottling of the skin, nor an appearance of dull-red spots. It should not cause pain, only a sensation of fullness of the engorged part. After forty-five minutes to an hour the patient may have some paræsthesia. In chronic cases, treated with firm application of the bandage, a treatment should last only forty-five minutes to an hour. If the proper degree of constriction is not obtained the bandage must be loosened or tightened as the case may be. The pulse should never be affected. After removing a bandage applied in this way, the limb becomes bright red, and arterial hyperæmia sets in. This reaction, whatever may be its physiology, whether due to a vasomotor paresis or to a specific "tissue thirst" (Bier), I believe is most important in the treatment of chronic cases. As yet it has received very little attention.

As said above, the application of the bandage in acute cases is in many respects similar to that in chronic cases. The bandage is applied very lightly so as to produce a mild venous congestion and œdema of the distal part. If a cellulitis is being treated such a bandage properly applied produces an exaggeration of all the local signs of inflammation, up to the production of an intensely red, "fiery red" œdema. The part never should be as blue as in the chronic cases, though occasionally there may be a tinge of blue in the deep-red coloration. This bandage should not cause pain, and usually relieves it. It remains in place for ten to twenty hours at a time, producing a marked swelling of the limb, and during the intervals between applications two to four hours daily the œdema is allowed to subside, elevation and massage (rarely) being employed to assist. It must be remembered that the fiery-red reaction in acute cases becomes less and less marked as the focus of inflammation is controlled. This lessening of the reaction is indicative of improve-

ment, and if it fails to take place Bier says an abscess that should be incised is present.

As the bandage remains in place in most acute cases for ten hours, in severer cases twenty hours, at a time, naturally its position must be shifted at successive applications to avoid pressure sores and atrophy of the deeper parts (muscles). It is advisable to select two levels and to apply the bandage first at one and then, after the pause between applications, at the other. If the second application be made distal to the first the bandage will have to be tightened repeatedly as the œdema caused by the first application disappears.

Another point to bear in mind is that the applications are gradually shortened as the cure progresses. Sudden cessation of treatment may lead to a recrudescence of the trouble, so that it is well to keep up the treatment for several days after the signs of inflammation have subsided.

Although in some cases the proper application of the constricting bandage may effect a cure without incision, it is advisable to make small openings into all pus foci before commencing hyperæmia treatment. *Whenever there is pus it should be evacuated by incision.* The incisions, however, should, as a rule, not be drained. *Gauze drains should never be used.* Occasionally rubber tubes are needed to keep the incisions wide open and to permit of the proper drainage of the artificial transudate into the dressing. In treating acutely inflamed parts with constriction hyperæmia, many fail to get good results because the part that is diseased is bandaged so firmly that an artificial œdema-hyperæmia cannot be produced. The best and simplest method of enveloping the treated part is without a bandage. The limb is covered with gauze and the whole is then surrounded with a towel that is pinned together without exerting any pressure on the diseased tissues. If the area has been incised a voluminous dressing will be required to soak up all the discharge, which, as said above, is markedly increased under this therapy. In such cases as the latter, it is advisable to give the patient plenty of fluid to take the place of all that is washed out through the incisions.

In the more acute cases, after removal of the bandage the products of the local inflammation, toxins, etc., may be swept into the general systemic circulation and lead to constitutional symptoms which were not manifest while the bandage was *in situ*. Chills, increase in temperature, headache, malaise develop occasionally. Severe or dangerous intoxication or sepsis, as dreaded by Lexer, I have not seen. The opinion of those who are using this constriction hyperæmia is gradually coming to the standpoint that I emphasized almost two years ago. All chronic cases that are treated with short applications may be so treated in the office or in the dispensary; whereas all cases that require protracted application must be carefully supervised and should be in hospital.

To illustrate the application of constriction hyperæmia I will cite several cases both chronic and acute.

CASE IV.—M., 15 years. Had been operated upon for acute osteomyelitis of the tibia. The wound had never healed, and as bone was felt at the bottom of the sinus another operation was performed to remove the dead tissue. After this a sinus persisted for many months over the head of the tibia, and exposed bone was felt at the bottom of the sinus. At this stage I began treating with constriction hyperæmia, using firm constriction for forty-five minutes, three times a week. The bandage was applied to the thigh just above the patella, and the leg was left exposed. The bandage was applied tight enough to produce a reddish-blue coloration of the leg without causing pain. Toward the end of the treatment the patient complained of numbness in his toes. While the bandage was in place, the discharge from the sinus increased. After removal of the bandage the leg became bright red. The sinus was dressed with a wet dressing. No drain was used. Under this therapy the sinus gradually closed and in a month or so no evidence of diseased bone was recognizable.

CASE V.—F., 60 years, had fallen from a ladder and received a compound fracture of her ankle, Pott's fracture. This became infected and was operated upon several times, pus being evacuated and bone removed. After four months of daily dressings with drainage the patient came to me. She had severe pain in her ankle and leg. She had no use of her foot, though its position was satisfactory. There was very little motion in the ankle joint. Sinuses ran down to the bone from all four aspects of the joint. There was chronic thickening with œdema of the ankle and foot. Drains were immediately discontinued and a firm constriction bandage was applied, twice daily, for forty minutes about the thigh. This produced a marked venous congestion and induced freer drainage from the tortuous sinuses. Pain rapidly disappeared and motion in the joint became freer. Gradually the sinuses closed after discharging several particles of dead bone. Daily hot foot baths aided in hastening the absorption of the infiltrating œdema about the ankle. Within six weeks of the beginning of treatment the ankle had assumed much more normal outlines, pain had ceased, fair motion had been restored, all but one of the sinuses had closed, and the patient was beginning to walk on her foot.

These cases illustrate the use of artificial venous hyperæmia in which the bandage is applied firmly. In the treatment of tuberculosis of bones and joints, in endeavoring to stimulate callus formation in pseudarthrosis, etc., this type of hyperæmia is employed.

CASE VI.—M., 40 years. No history of injury. Developed an acute painful swelling of right knee. Knee joint was full of fluid and very tender. Temperature 104.5° and pulse 120–126. Aspiration of the knee joint removed a thin purulent fluid which contained streptococci as shown in spread and in culture. A mild application of the rubber bandage on the middle of the thigh was begun at once. The bandage was tightened until the leg became red. It was left in place for twenty hours at a time and a massive œdema developed. During the four hours that the bandage was off, the leg was elevated and much of the œdema disappeared. During this period the patient's temperature gradually rose and then fell a little as the bandage was reapplied at another level. For several days the bandage was employed for twenty hours at a time, and then the periods were shortened as it became evident that the therapy was proving effective. Evidence of this was furnished by the gradual lytic fall of the temperature and the diminution of pain and of tenderness. In the course of two weeks the temperature became normal, and the knee was freely movable though still somewhat distended with fluid. It is interesting to relate that, though the inflammatory condition in the knee joint cleared up so completely, two abscesses developed above the joint leading down to the fascia lata. These were small foci and in no wise connected with the joint. Judging from their situation, I suspect they were occasioned by the pressure of the rubber bandage. This is all the more striking as it is difficult to understand why the hyperæmia cures the original focus and still does not prevent such a complication as the above in the hyperæmic area. After incision these small abscesses closed, and in less than a month the patient was discharged with a perfect limb.

CASE VII.—M., 13 years. Shot three days prior to admission, bullet entering skin over left knee joint. Pain, swelling, tenderness, impaired function, and fever developed. When brought to the hospital the patient had a temperature of 103° and all the signs of an infected knee joint full of fluid. The joint was opened by two lateral incisions and a large quantity of pus was evacuated. The bullet was found in the intercondylar area. The capsule of the joint was closed on both sides except for two small openings at which rubber tubes were sewn in place. The skin was closed similarly except at the site of the drainage tubes. An ample dry dressing was loosely applied and Bier's hyperæmia was immediately instituted. The bandage was applied lightly, ten hours

on and two hours off, then on again. The discharge was copious, and after two days active and passive motion was begun. This assisted in expelling the transudate that continuously collected in the joint and ballooned the cavity. After three days the tubes were removed and the same therapy continued, gradually cutting down the periods of constricting hyperæmia, so that within a week the patient's temperature was practically normal, and within three weeks the patient was discharged with a normal knee joint.

CASE VIII.—M., 20 years, had been ill for almost a week with very marked swelling of the left leg up to the knee. There was fluctuation in the calf on the outer and inner sides. Here small incisions were made and over a pint of pus was evacuated from the abscess, which extended from the popliteal space to the os calcis. After drainage tubes had been placed in the incisions to keep them wide open and a loose dressing had been applied, hyperæmia of the mild constrictive type was at once begun. A marked red œdema developed under the bandage, which was used as in Case VII., ten hours on and two hours off. The drainage was astonishing. The tubes were rapidly shortened, and as the local conditions improved the treatments were shortened. In less than three weeks the patient's huge abscess cavity had completely closed and the leg was a normally useful member.

These last three cases will demonstrate in a general way the method of employing this type of hyperæmia. The main points in technique that they emphasize are: (a) Light, painless application of the bandage so that the part becomes œdematous and red—looks more inflamed than before; (b) Incisions where there is pus; (c) Loose and copious dressings; (d) Gradual shortening of the periods of treatment; (e) Tube drainage only if necessary to make incisions gape.

Before discussing the advantages and the various criticisms of these methods, that are grouped under the name of Bier's hyperæmia, it is essential that an analysis be made of the various conditions in which these types of hyperæmia have been used. The total number of treated cases is naturally beyond computation, as so many are using the method. A review of the conditions in which hyperæmia has been used, with a description of the results obtained, naturally must precede a discussion of the relative advantages of these over other methods.

Arterial Hyperæmia is particularly useful in conditions associated with or due to poor local circulation. As it relieves pain and assists absorption, it is also used when these activities are required.

Neuralgia. The use of heat is an old household remedy in various types of severe pains, and the hot-air douches are an effective method of employing heat. These are employed in all types of neuralgia, e.g., facial, sciatic, and they undoubtedly bring relief and occasionally they may cure. How often they effect a permanent result cannot be said with any accuracy.

Chronic Rheumatism. The use of superheated air in this condition is a well-recognized therapeutic agent, and there can be no denying its beneficial action even if it does not regularly prove effective. This method of treatment in such cases obtains almost everywhere. In this condition the artificial hyperæmia leads to absorption as well as to relief of pain. Bier emphasizes the fact that if many joints are treated, each joint should be exposed a short time, or the worst joints should be selected and treated for thirty minutes; for very protracted treatments of each joint are liable to lead to constitutional effects, neurasthenia, anæmia, and general enfeeblement. After using this therapy for several weeks or months it is discontinued, and for one to four weeks the joints are enveloped each night in wet dressings or in irritating, hyperæmia-inducing fomentations. Bier prefers constriction hyperæmia to this arterial hyperæmia in the acute exacerbations of chronic rheumatism and in involvement of smaller joints, e.g., elbow, hand, or finger.

In arthritis deformans Bier believes he has seen good results. Personally I have seen no real benefit in this condition from arterial hyperæmia, though pain may be relieved temporarily. Others, including Habs, Bum, and Leyden, have seen good results in chronic rheumatism, but nothing in arthritis deformans.

Post-traumatic stiffness of joints is beneficially influenced by hyperæmia. Bier uses hot air in these cases and obtains rapid improvement. Motion increases and pains cease. Everybody has seen excellent results following the use of hot baths that induce well-marked hyperæmia, so that it is needless to waste many words on this subject. In addition to hot-air therapy Bier employs the large orthopedic suction cups to stretch the joints, and also constriction hyperæmia, as will be seen later.

In scoliosis Klapp has employed hot-air treatment to assist in loosening the more or less fixed vertebral column. This combined with gymnastic exercises he considers the best therapy thus far discovered.

Gonorrhœal rheumatism in the more chronic stage is beneficially influenced by arterial hyperæmia, according to Bier. In the more acute stages constriction hyperæmia is indicated. In these difficult cases hyperæmia ought surely to be tried, as it will relieve frequently. It is, however, no panacea and, in my experience, frequently fails to do anything just when most needed.

In the reparative stage following acute infectious osteomyelitis and suppurative tenosynovitis, short daily applications of hot air are beneficial in stimulating rapid repair of the injured tissues. Hot baths do practically the same thing and are simpler. In the latter way most surgeons have employed arterial hyperæmia for this class of cases a long time.

In senile and diabetic gangrene the use of arterial hyperæmia will frequently lead to a rapid demarcation, and if the process is just beginning such hyperæmia may save the limb. In the form of hot baths this type of hyperæmia has long been used, especially in the limited processes, e.g., in gangrene of a toe or in diabetic mal perforant. In such cases short applications of superheated air beginning with low temperature may produce practically a *restitutio ad integrum*.

In skin conditions, e.g., frost bite, chronic eczema, psoriasis, arterial hyperæmia induced by hot air has led to good results.

To hasten absorption of extravasated blood, œdemas, chronic hydrops (non-tuberculous) of joints, hæmarthrosis, Bier employs hot-air hyperæmia and obtains excellent results. He mentions a large number of cases in which this therapy was employed effectively. In chronic œdema of the lower extremities due to varicose veins, and in varicose ulcers, good results follow arterial hyperæmia. I have regularly used cardiac stimulants to improve the local circulation, and these with nitroglycerin probably worked much in the same way as hot-air therapy. In recent thrombotic cases Bier advises against arterial hyperæmia. In cases of thrombosis of the deep veins it is well to be chary in the use of superheated air, as in one case of thrombosis of the femoral vein treated in this way six months after the thrombosis Bier lost his patient from a pulmonary embolus.

In fresh fractures and in fresh injuries to soft parts, Bier uses daily hot-air therapy for one hour, as it hastens absorption of extravasated blood, etc., and he believes it surpasses massage in efficacy.

Suction Hyperæmia.—This type of hyperæmia is used in a great variety of conditions both acute and chronic, both in general surgery and in the specialties. It has been received with great favor by most of the profession and is destined to be a useful therapeutic agent. Among the more important conditions in general surgery in which it has been successfully employed are the following:

In prophylaxis against infection this type of hyperæmia is as old as the birth of the higher animals, that have always employed their lips to suck freshly inflicted

wounds. To prevent infection of incised or of not over-deep perforating wounds there is no better agent than suction hyperæmia. Its regular use undoubtedly will obviate many an infection and save many a patient and many a surgeon much pain and loss of time.

In stitch-hole infections there is no therapy so effective, so simple, and so rapidly curative. Incisions are rarely required, and extensive abscess formation is usually prevented by an early use of suction hyperæmia.

In abscesses, furuncles, acne, infected wounds, cellulitis of fingers or of hand one almost regularly succeeds in curing the condition with small incisions into the pus foci and regular use of suction hyperæmia. In some of the more extensive cases of cellulitis, occasionally also in cases of paronychia, the mild application of a constricting bandage—constriction hyperæmia—is decidedly more effective than suction hyperæmia. In those cases of deep infection of the fingers—so-called paronygium—constriction hyperæmia should be regularly employed, as some have reported poor results with suction hyperæmia.

In suppurative mastitis suction hyperæmia has scored a triumph, even though in every single case it may not be successful. Instead of the old radial incisions and copious gauze drainage, small incisions into the pus pockets, and suction hyperæmia with large cups encompassing the whole breast, lead to rapid cure without mutilation and painful dressings. In puerperal cases the milk should be withdrawn before each hyperæmization of the breast. Occasionally after one focus has been healed a fresh one develops and must be treated in the same way. The end result is almost regularly excellent both functionally and cosmetically.

In carbuncles, especially the non-diabetic, the best of results have been published. In these no broad incisions are demanded. Suction draws pus out of the many suppurating areas and a rapid cure is effected. (Bier, ten to fifteen days.)

In diabetic cases special care must be observed, as the tissues may not bear this therapy. Grube and Körte have employed artificial hyperæmia in diabetics without injury, whereas Colley saw gangrene of the skin following its use. The last word has not been spoken concerning this group of cases, but the varied results surely prompt us to be very cautious.

In acute suppurative adenitis, especially in buboes, one frequently obtains rapid results after incising the purulent focus. If many glands are involved, and there are multiple pus foci scattered through the different glands, hyperæmia may fail to accomplish anything. In these cases preliminary use of poultices followed by small incisions and then by suction hyperæmia with large cups will usually prove effective. In some cases every attempt will fail and recourse to wide incisions and excision of the suppurating glands will be finally necessitated.

In acute bursitis, especially suppurative bursitis, suction hyperæmia works well. If pus is present a small incision followed by hyperæmia will lead to excellent results, painlessly and rapidly.

In infected hæmatomata and in contusions suction hyperæmia is very effective. In infected hæmatomata suction hyperæmia, after a small incision, is exceptionally useful. The suction evacuates clots and fluid blood rapidly and painlessly. In black eyes this therapy leads to rapid oxidation of the extravasated blood and prompt absorption.

In more chronic inflammatory conditions, e.g., chronic sinuses both tuberculous and non-tuberculous, suction hyperæmia has scored a distinct success. Bier and Klapp regularly use it in fistulous bone and joint cases of tuberculous causation. In sinuses leading to tuberculous glands I have seen rapid healing without excision of the gland. I have seen good results in fistulæ about the anus. Applications over tuberculous glands through the skin, if the glands are subcutaneous, may be of use. I have seen such glands become smaller and firmer under this therapy.

In keloids Bier and others report absorption of the tumor. Although I have failed signally in this condition, a positive result is more valuable from a therapeutic standpoint than a negative one. In view of the successes of Thomas and of Bier, suction hyperæmia should be tried in keloids.

In the removal of foreign bodies, *e.g.*, pieces of glass, splinters, etc., it is almost self-evident that suction will assist, not only in drawing out the foreign matter, but also in producing a local immunization and thus prevention of infection.

In orthopedic surgery the very large cups are employed. So far as the use of these large suction cups is concerned, very few have had any experience with them, so that we shall have to confine our remarks to the statements of Bier and Klapp. They use these large cups to stretch joints that have been rendered more or less stiff as the result either of trauma or of rheumatism. The combined action of the hyperæmia plus pressure of the atmosphere produces marked changes and restores excellent motility. Bier advises against the use of these orthopedic cups in joint tuberculosis so long as the disease is active. In tuberculosis of the knee with marked flexion deformity, however, Bier employs these cups to assist in overcoming the deformity even though the tuberculous process is not quiescent.

In nasal, aural, and ophthalmological surgery this type of hyperæmia has been employed to some extent, but until more publications are forthcoming no final verdict as to its usefulness will be possible. In both the nose and the middle ear anatomical conditions are such that it is not easy to duplicate the suction hyperæmia induced on other surfaces. In various types of tonsillitis good results have been reported. Of eye conditions treated in this way very few reports have been published.

In gynecology suction hyperæmia has been employed quite extensively. Its field of usefulness is still undetermined. It has been used in chronic endometritis, perimetritis, and metritis, with more or less success. In amenorrhœa the results have been variable.

Constriction Hyperæmia.—As was said in the discussion of the technique of this type of hyperæmia, the rubber constricting bandage may be applied very lightly in acute cases, and more firmly, producing more marked venous congestion, in the treatment of more chronic cases. In the following conditions the firm application of the bandage has been employed to induce a marked venous hyperæmia and thus a cure of the pathological condition. Later the applicability of the milder constriction hyperæmia will be discussed.

Pseudarthrosis.—In delayed union of fractures due to deficient callus formation, constriction hyperæmia has frequently been of great benefit. This use of a constriction proximal to the threatened pseudarthrosis is very old. Ambrose Paré, Duremreicher, and Nicoladoni recommended it. Helferich in 1881 used this type of hyperæmia for insufficient callus formation after fracture; also in insufficient involucrum production after bone necrosis. Thomas has made use of it to obtain firm union in fractures.

This method of treating the condition under discussion is simple. The part is bandaged in flannel up to the site of the fracture, and proximal to the fracture the rubber bandage is applied. This technique localizes the activity of the venous congestion at the point of fracture. Of course this application is not always feasible if the fracture is so situated that a distal flannel bandage cannot be used, nor is it absolutely necessary.

In view of the painlessness, simplicity, and lack of danger of this method it should regularly be used, and judging from my own experience, employing it as I do in all delayed unions as a routine procedure, I believe patients very frequently will be spared more serious, uncertain, and dangerous methods which are used to accomplish the same result.

In chronic suppurating osteomyelitis, especially cases that have been operated upon or cases following compound fractures, venous congestion without the use of

drains in the sinuses, which are regularly present, leads to most gratifying cures. The illustrative cases cited above are instances of the beneficent action of venous congestion in this class of cases. The necrotic bone, provided, of course, the size of the sequestrum permits, is after a rapid separation from healthy tissue discharged through sinuses. Congestion leads to better drainage from within, and after removal of the bandage the reactive hyperæmia in turn has a good effect.

In tuberculosis of bones and of joints the therapy under discussion was first tried. As said under suction hyperæmia, fistulous cases are treated with suction and constriction hyperæmia. This therapy has led to excellent results not only in Bier's clinic, but also in the hands of v. Eiselsberg, Kocher, Habs, Luxembourg, Tillmanns, and Henle (Mikulicz). There seems no reason to doubt the efficacy of this therapy in this class of cases, from what I have seen in my own work. To get a good idea of Bier's results it is worth while enumerating his series of cases:

1. Carpal Tuberculosis; 17 Cases. Of these 4 had fistulæ. In 5, abscesses developed during the treatment and were opened. Results: Fifteen cases cured, 3 had perfect motion, 2 were improved. Average duration of treatment twelve months.

2. Elbow-joint Tuberculosis; 11 Cases. Five had fistulæ, 8 developed abscesses that were incised. Results: Eight cases cured. Normal motion in no case, though in all it was adequate. The worst result showed a mobility of from 50° to 115°.

3. Tarsal Tuberculosis; 13 Cases. Eight had fistulæ. In 6 cases, abscesses had to be opened during treatment. Results: Eight cured, 3 improved, 1 unimproved, 1 came to amputation. Perfect motion in 3 of the cured cases, satisfactory in the others. Duration of treatment averaged ten months.

4. Knee-joint Tuberculosis; 5 Cases. One had fistula. Results: Three were cured, 2 with perfect motion, 1 was fixed in good position, 2 were improved. In 8 other knee cases after short trial with hyperæmia Bier did a resection.

5. Shoulder-joint Tuberculosis; 1 Case. Result: Cure with perfect motion.

From these data it is evident that this conservative method of treatment leads to excellent results in carpal, tarsal, and elbow tuberculosis. In the knee joint the results of this therapy are not good.

While employing this method of combating tuberculosis the involved part is not immobilized, as one of the objects of this whole therapy is to obtain a good functional limb. In the lower extremity I do not feel ready to abandon removable splints. One cannot gainsay that Bier's treatment requires a great deal of time, nine months on an average, but all conservative measures in these cases are very slow in effecting a cure.

This therapy is contraindicated, according to Bier, in (1) amyloid degeneration; (2) severe pulmonary tuberculosis; (3) large distended pyarthrosis (knee); (4) faulty position, when operation will give better end results. In tuberculosis of bones Bier regularly operates unless such a procedure would interfere with the function of the part. In cases of spina ventosa Klapp has been successful with suction hyperæmia.

Tuberculosis of the testis Bier has subjected to venous hyperæmia by tying a rubber band or tube about the root of the scrotum. If both testes are involved both are treated simultaneously—otherwise only the diseased organ. The hyperæmia is induced for one to three hours daily, and the scrotum is supported by a suspensory. Bier has seen the best results in fistulous cases. He has published no convincing data up to date, so that it is proper to reserve judgment, especially as he says the therapy is less efficient in beginning tuberculosis of the epididymis. He recommends the same hyperæmia therapy for tuberculous disease of the tendon sheaths and skin, and for lupus.

In stiff joints following contusions, fractures, healed cellulitic area, etc., I have been pleased with

this therapy. Bier recommends the mild application for ten to twenty hours at a time. This I have not employed, as these patients are not willing to give up the time necessitated by such long applications. With three-quarter to an hour treatments, and marked venous congestion, good results can be obtained and the patient need not enter a hospital for surveillance. While the bandage is in place, active and passive exercises are carried out and motion is gradually increased by stretching the hyperæmic tissues. Because of the anæsthetizing effect of the hyperæmia the parts can be more readily moved and the involved tissues stretched with less discomfort.

In vague joint cases in which the diagnosis is obscure, as well as in old rheumatic cases and chronic gonorrhœal joints, this firm application of the bandage can readily be employed without putting the patient in a hospital. Bier favors long applications of the milder constriction hyperæmia. Which method is better I cannot say. The method I have used is simpler and liable to appeal to the patient, if the results are equally good.

In addition to vague joint cases, there are many other post-traumatic vague neuralgic or painful conditions in the extremities which, strange to say, are benefited by this therapy. The diagnosis is never made, but the patient gets well.

It is in interpreting the curative effect of the milder constriction hyperæmia that one must be particularly guarded. There is no doubt that one sees most astonishing results in the most diverse acute conditions under this therapy, and to be strictly scientific in the face of these is often practically impossible. In the following conditions it has been repeatedly employed, and found favor.

Prophylaxis against Infection. As mentioned under the uses of suction hyperæmia, in this field we have a very useful agent in artificial hyperæmia. While suction hyperæmia is useful in the smaller injuries, in the more extensive wounds of extremities constriction hyperæmia must be employed. As a prophylactic agent hyperæmia has proven to be our very first and most effective agent. Prior to its introduction the surgeon did little or nothing in the treatment of fresh wounds that could be interpreted as truly prophylactic against infection. If a patient acquired a compound fracture and the ends of the bone pierced the skin, the surgeon could rely on seeing an infection, perhaps a most serious infection that would lead to incision and drainage, at times to amputation or to death. Now in hyperæmia, in the mild constrictive type of hyperæmia, I believe we have at last an agent that will produce a local immunization and prevent in many cases the development of a serious or even slight infection. The most striking instance of the efficacy of this therapy that I have seen was in a case of fracture of the fibula and tibia. Both bones perforated the skin, and their fractured ends were thoroughly contaminated. After replacement of the broken bones Bier's hyperæmia for twenty-hour periods was applied for at least ten days and a perfect recovery took place, as far as infection was concerned. Another series of cases in which I have employed this type of hyperæmia to prevent trouble are the post-operative cases mentioned below.

This use of hyperæmia I feel sure will be a boon to humanity—it marks a distinct advance. As yet the literature has paid but scant attention to this subject.

Acute Inflammations: (1) Cellulitis, lymphangitis; (2) Tendon-sheath phlegmon; (3) Suppurative arthritis; (4) Acute osteomyelitis; (5) Erysipelas.

The use of mild constriction hyperæmia in the above inflammatory conditions is one of the most important developments in this field of therapy. Bier has seen the most remarkable results in all these conditions, but even he must admit that hyperæmia may not be effective in some cases. To any one who has read the literature of this subject, even if he has not employed the method and demonstrated to his own satisfaction the effects of

this therapy, it will be clear that hyperæmia accomplishes a great deal that our older methods did not accomplish as simply, as painlessly, and as rapidly. Still, until cases are reported with bacteriological examinations it will remain undecided whether hyperæmia has an equally beneficent effect against all invading bacteria. Lexer deserves credit for bringing out this point when he claims that hyperæmia does not work successfully against severe streptococcic infections. Although I have repeatedly seen this therapy cure infections due to streptococci, still we must in the future study this problem and determine whether our new agent is as effective against one type of organism as another.

Bier believes he has been able to cut short beginning suppurative processes with this method. His cited cases are not so conclusive as they should be, as I have seen similar pyæmic deposits disappear without therapy just as rapidly. In fact only recently on one patient who had pyæmic deposits in several extremities I compared hyperæmic treatment with no treatment at all. The different deposits did equally well. Hyperæmia was no more effective than leaving nature alone. Though I have not seen very severe cases of cellulitis disappear without suppuration, I have seen milder cases behave in that way. There is no doubt in my mind that this therapy will cut short many an acute post-operative infection of an extremity. Here it is the only agent we can avail ourselves of, and I have repeatedly employed it to prevent suppuration. It is particularly useful after joint resections, and in these it might even be used prophylactically to insure a good result.

Good results following the use of this constriction hyperæmia in acute inflammatory conditions have been reported by Habs, Körte, Sick, Stich, Danielsen, Bardenheuer, Heidenhain, Lexer, Heller, Haaster, Losser, Derlin, v. Brunn, and others. I have used Bier's methods in considerably more than four hundred cases, of which over one hundred were acute inflammations, and I have usually seen excellent results. The great difficulty that we meet with is in deciding whether the results are due to the hyperæmia therapy. I have frequently been in doubt and have hesitated to ascribe all the *post hoc* developments to our therapeutic agent. Unfortunately, parallel cases and parallel observations cannot be studied. Although one has the impression that hyperæmia almost regularly benefits, still it will require time and much more experience to furnish positive and irrefutable proof.

Cellulitis and lymphangitis cases seem to do well under this therapy. The pus foci naturally are opened, by small incisions if possible, before this treatment is begun, and, as said above, no gauze drains are employed, as gauze devitalizes the tissues with which it comes in contact. There is great unanimity of opinion that staphylococcus infections respond nicely to this treatment, whereas streptococcus infections may be less easily controlled. Lexer and Sick have emphasized the latter.

Tendon-sheath infections have been very successfully treated. The avoidance of gauze drainage and the constant bathing of the tendons in plasma frequently save tendons which would under the old therapy become necrotic. Bardenheuer, after extensive trial, is most enthusiastic, having had exceptionally good results. He states that if nothing else had been effected by this new therapeutic agent, its excellent effects in tendon-sheath infections would establish a place for it in our therapeutic armamentarium.

Suppurative arthritis cases have frequently done well. As shown in one of my illustrative cases, the joint may not require incision, though usually it will be safer to aspirate and wash out or even to incise whenever there is pus. In addition to Bier, Bardenheuer, Habs, and many others have reported good results.

In acute osteomyelitis considerable difference of opinion exists. Some have had good results, others have not. Garré's advice to open the bone in the usual way will probably be followed until more convincing proof is presented that hyperæmia with small incisions, or as-

piration, or hyperæmia alone can effect a cure. I personally am a little loath to follow Bier in this field, though he reports some remarkable results, in which the focus in the bones healed, and frequently without necrosis. For when the process has extended from the marrow into the bone itself, I fail to see how we can produce an adequate hyperæmia in the diseased tissue. It may be possible to effect an inflammation that is limited to the marrow, though even here it must be difficult to induce hyperæmia and œdema at any but the earliest stage of the disease.

In erysipelas the claims of hyperæmia are even more doubtful. Bier was inclined to think it useful in this condition. Now even he is in doubt. Hochhaus and Sick have been pleased with its effect. In my experience some cases get well rapidly under this treatment and others are not affected. Those that get well rapidly frequently show a lytic fall in temperature, which is about the only symptom that might induce one to ascribe the result to hyperæmia; but as many cases of erysipelas behave in other points just as those treated with hyperæmia, it surely is dangerous to express a favorable view of the therapy in these cases. Moreover, it has frequently been noted that acute inflammatory cases develop erysipelas under hyperæmia therapy. Provided these are real erysipelas cases this would speak against the efficacy of hyperæmia therapy in such a condition.

Acute Conditions (Inflammatory) of the Head. Under these are included mastoiditis, otitis media, parotitis, parulis, meningitis, lymphadenitis, coryza, tonsillitis, dacryocystitis. Bier says in all these conditions he and others have seen good results. Here the bandage or webbing surrounds the neck and produces thus a hyperæmia of the distal parts. It is even more difficult to judge of the effect of the therapy in these cases than in most of the other inflammatory diseases just mentioned. Here prognosis is particularly difficult, for it is almost impossible to say accurately what would happen without hyperæmia. In this category of cases, scepticism has every right to an excellent hearing. How frequently patients with mastoid symptoms get well without surgical intervention after they have been persuaded that they should go to the hospital for operation! It is more than difficult to understand how an adequate œdema and hyperæmia can be produced in the mastoid, especially when its cells are filled with exudate. Here we encounter the same difficulty as mentioned under acute osteomyelitis cases. From what I have seen of the results of hyperæmia treatment in the extremities, I see no reason to doubt that in inflammation of the soft parts and of the mucosa of the middle ear and of the nose, etc., good may be effected here also.

Chronic rheumatism, stiff joints following injury, gonorrhœal joints are treated by this mild constriction hyperæmia by Bier. As mentioned previously, Bier employs long applications of the constricting bandage for the acute attacks of chronic rheumatism and also for involvement of the smaller joints. He treats stiff joints similarly or with superheated air (*vide infra*). As said previously, I have had good results in these cases treated in the dispensary with short applications and marked venous congestion. In gonorrhœal joints the constricting bandage may at first increase the pain (Bier), but if the patient can be made comfortable this soon diminishes and the inflammation will subside. Opinions as to the efficacy of this therapy in all kinds of gonorrhœal joints are still at variance. As some cases seem to respond, it surely should be given a fair trial.

In malignant œdema this type of hyperæmia should be employed. Both experimental and clinical work have demonstrated its efficacy against anthrax.

In the following conditions Bier has employed mild constriction hyperæmia with some success: (1) acute gout, (2) insect bites, (3) chorea, (4) epilepsy, (5) subcutaneous hemorrhagic extravasations, (6) chronic headache. There seems to be some justification for his

claims in acute gout, in insect bites, and subcutaneous hemorrhagic extravasations. The other conditions, however, require more study and further trials before a favorable opinion can be given.

Further Possibilities of Hyperæmia Therapy.—Pulmonary Tuberculosis. It was quite natural that an attempt should be made to influence tuberculosis of the lungs. Both the autolytic material and Bier's clinical material seemed to point the way to applying hyperæmia in this condition. The experience with bone and joint tuberculosis has demonstrated the value of venous congestion in this disease, and it would seem probable that pulmonary tuberculosis might respond to similar therapy. Unfortunately, as yet there is no method of producing a venous congestion in the pulmonary circuit, as emphasized some pages back. Even Bier admits that the blood in a congested lung must be mainly arterial, as it is rapidly arterIALIZED in the pulmonary capillaries. Moreover, experience has shown that arterial hyperæmia is ineffective in bone and joint tuberculosis. Despite this evident contradiction, despite the fact that clinicians in testing the effect of hyperæmia in pulmonary tuberculosis are employing arterial hyperæmia, which is ineffectual in bone tuberculosis, and are not producing a marked venous hyperæmia, still their work may develop something of value in the treatment of this disease.

Kuhn's mask, which compels the patient to breathe under difficulty, inspiration against resistance, expiration unimpeded, producing a suction hyperæmia in the lungs, is used for the treatment of pulmonary tuberculosis. Whether this will lead to any definite results time and careful observation alone will tell.

Suppurative meningitis has always appealed to me as likely to respond to constriction hyperæmia, provided the exudate and transudate are very frequently withdrawn or drained from the subdural space. If a mild constriction hyperæmia of the head be induced by a bandage about the neck, the brain and meninges become hyperæmic and displace the cerebrospinal fluid that is within the cranium into the non-compressed spinal column. Such endocranial hyperæmia produces in this way a marked increase in pressure in the spinal fluid. If in cases of acute meningitis this spinal fluid were frequently withdrawn, or constant drainage were made in the lumbar region, we might be able to influence the inflammatory condition, just as we do in peripheral infections. Cases of compound fracture of the skull and of basal fracture (W. Meyer) might be treated prophylactically with hyperæmia with or without lumbar puncture, to insure against meningitis.

As yet the publications in this field are few and not in any way conclusive. In the few cases treated allowance has not been made for a proper hyperæmization of the endocranial structures by frequent lumbar puncture, and till that is done nothing final may be said on this subject.

In addition to these two conditions many others will probably suggest themselves as amenable to hyperæmic therapy. All new therapeutic agents when looked upon from every standpoint will be used in a variety of conditions for which they were not originally suggested, and perhaps will prove particularly effective in some of these.

Contraindications to the Use of Hyperæmia; Dangers.—These cannot be gathered and stated dogmatically at the present time. Superheated air must be used cautiously in all conditions associated with lowered vitality, and should not be employed in cases of thrombosis of the veins. Suction and constriction hyperæmia should be used very cautiously in diabetics. In very severe streptococcus infections one should be guarded in relying exclusively upon these agents. In cases that do not respond to constriction hyperæmia this should be stopped. This applies particularly to those acute cases in which there does not seem to be sufficient power to check the infective process.

The methods above described, provided these contra-

indications are avoided and provided the technique is perfectly applied, have very few dangers. Erysipelas may develop in the treated part. At the site of the bandage necroses of fascia or skin occasionally develop. Once I saw a deep-vein thrombosis at the site of the bandage in a streptococæmia case. Others have seen this also.

If the technique is faulty, naturally serious accidents may occur. Whenever a bad result is reported there is a distinct tendency to attribute it to faulty technique. No doubt many poor results are due to this, but the tendency to attribute all these to technical failures is a mistake. Hyperæmia is surely no panacea and not infallible, so let us group all bad results together, whether due to the operator or the method, till we have some definite criteria to distinguish between these two sources of trouble. In practice the two are associated—the hyperæmia demands an operator, and the therapy must be viewed in that light, rather than as a simple hyperæmia unit.

Criticisms of Hyperæmia are based chiefly upon its therapeutic use in acute infections. The application of arterial hyperæmia is rather generally accepted at its proper value. As hyperæmia in acute infections marshals Nature's forces to fight the invader, it avails itself of Nature's weapons alone. If these are inadequate it will fail to win the battle. That is self-evident. Fortunately these forces are usually adequate.

Lexer's criticism of Bier's method in acute cases is more spirited than sound. He indulges in many theoretical points which were brought together to overwhelm this therapy just at the time that it was creating such a furor in Germany. Lexer claims that hyperæmia assists in just those cases where older methods succeed as well. In severe cases it is dangerous, as it allows of a local culture of bacteria and a local destruction of tissues by the bacterial endotoxins. These points are still unproven, though, as frequently said in this essay, great caution must be observed in severe streptococcus infections, lest, relying on hyperæmia too much, the patient's interests suffer.

In the treatment of peripheral tuberculosis, Mosetig Moorhof has taken the position that this hyperæmia therapy is dangerous, as it may lead to a dissemination of the disease. As yet no cases have behaved in this way.

Another and more practical objection to Bier's methods relates to the time they demand. No suction treatment can be properly carried out in less than forty-five minutes. Constriction hyperæmia in acute cases requires continuous watching for hours. This is a hardship for the busy surgeon, and will be one of the chief obstacles to the wide use of Bier's methods. By teaching patients how to cup themselves, by treating a number simultaneously, by placing others in hospitals under the eyes of the house staff, we can avoid this difficulty. Those who are not so situated that they can do these things will be slow to take up these new methods, unless they dread the older methods of long incisions which Bier has supplanted in the treatment of most cases.

Advantages of Bier's Hyperæmia.—It is proper to close this essay by a brief reference to the advantages of the methods under discussion. As they have already been touched on in the course of this essay, it will suffice to enumerate them briefly.

Arterial hyperæmia has a field of its own, and there are no therapeutic agents that have proven more effective in the conditions for which it is used.

Suction hyperæmia in acute inflammatory cases avoids long incisions and painful and injurious gauze packing, and leads to a cure more rapidly than older methods. In prophylaxis both types of hyperæmia are distinct additions, as prior to Bier's discovery we knew no method of avoiding infections after injuries. Like suction hyperæmia, constriction hyperæmia does away with long incisions and their resulting scars; it also frequently prevents necrosis and sloughing of tendons where older methods failed. Constriction hyper-

æmia in acute infections usually shortens the time of illness.

Even if venous hyperæmia did no more than provide excellent drainage from within outward, in acute infections I should employ it regularly as it avoids all painful manipulation of the infected area. As it accomplishes much more than drainage, I am all the more glad to make use of it.

In the more chronic conditions both suction and constriction hyperæmia are very useful in just such cases as are mentioned in the previous pages, and that are frequently encountered wandering from pillar to post looking for relief.

With such marked advantages over older methods, with a broad usefulness in conditions that up to date have not been amenable to therapy, it does seem likely that artificial localized hyperæmia, both arterial and venous, has come to stay, both as a boon to mankind and as an interesting field for scientific study.

Edwin Beer.

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INTESTINES, TUBERCULOSIS OF.—This is the most common specific infection of the intestinal tract. It occurs both as a *primary* and a *secondary* process, the lesions being rarest in the duodenum and increasing in frequency toward the ileo-cæcal valve to become more rare in the large intestine. In the lower part of the ileum, particularly on the upper surface of the ileo-cæcal valve, tuberculous lesions are found in nearly all cases (about 90 per cent.) of advanced pulmonary tuberculosis. In rare cases the small intestine may be entirely free from the disease, while the colon and rectum are extensively involved. Still more rarely isolated

tuberculous ulcers are found in the duodenum without the occurrence of other intestinal lesions.

In the *primary* form the infection occurs through the ingestion of tubercle bacilli in the food or through the swallowing of saliva containing bacilli that have entered the upper respiratory tract with the dust of the air. *Secondary* intestinal tuberculosis is nearly always due to the swallowing of sputum containing tubercle bacilli derived from pulmonary lesions. In a small number of cases the intestinal lesions are secondary to tuberculosis of the upper respiratory tract or upper portion of the alimentary tract, or they may be metastatic in origin from primary foci situated in any part of the body.

PRIMARY TUBERCULOSIS OF THE INTESTINES.—A very great difference of opinion exists as to the frequency of primary intestinal tuberculosis. The experience of different pathologists varies so greatly, even when in the same city and under apparently similar conditions, that no certain conclusion can be drawn from the statistics as they stand at present. The majority of German pathologists regard primary intestinal tuberculosis as rare, although several competent observers rate its occurrence as from 5 to 25 per cent. of all cases of tuberculosis in young children. English writers believe that primary tuberculosis of the intestines is not infrequent in children, while in America individual experience and the resulting opinions vary greatly. The total number of reported cases of undoubted primary intestinal lesions is very small, however, in proportion to the great frequency of deaths from tuberculosis. The question of the infrequency of primary intestinal lesions does not, moreover, affect that concerning the intestines as a frequent avenue of entrance of tubercle bacilli, since it has been shown that tubercle bacilli may pass through the intestinal wall without exciting there any lesion. Further, in many cases the seat of the primary infection may be wholly overshadowed by the more rapidly developing secondary or general conditions.

Either the bovine or the human strain of tubercle bacillus may cause primary lesions in the intestine, the former entering the body in milk or its products, while the latter enters with the dust of the air and is swallowed in the saliva. The bovine form is more likely to occur in children, and a number of undoubted cases of primary intestinal lesions due to bovine bacilli have been reported. It is possible that the bovine form is more common than is generally believed. The relative freedom of the intestine from tuberculous lesions as compared to the greater frequency with which the mesenteric glands are involved may also be due to the fact that a slight tuberculous lesion of the intestine may disappear leaving no trace, while the secondary process in the lymph nodes increases in severity and appears as the primary localization of the disease. The greater permeability of the mucosa of the intestine in children is also a factor to be considered.

SECONDARY FORM OF INTESTINAL TUBERCULOSIS.—In the later stages of pulmonary tuberculosis, or less frequently at an early period of development of the disease, involvement of the intestine results from the bacilli swallowed in the sputum or saliva. The lesions usually occur in the lower part of the ileum and involve particularly the lymphoid structures. The bacilli in the intestinal contents adhere to the surface of the mucosa and pass through it, being carried most probably for the greater part by leucocytes to the lymph-follicles. Various authorities assert that the intestinal lesions always begin in the lymphoid tissue, but very minute microscopical tubercles may be found in the stroma of the mucosa or submucosa entirely independent of the lymphoid structures.

GENERAL PATHOLOGY OF INTESTINAL TUBERCULOSIS.—Tuberculosis of the intestine occurs in two forms, the *ulcerative* and the *hyperplastic*. The *ulcerative* form is by far the more common. The bacilli gaining entrance into the stroma of the mucosa or into the lymphoid tissue of the solitary follicles or Peyer's patches cause first a local degeneration or necrosis which is followed

by the formation of a characteristic milary tubercle. These may be isolated or multiple, and in the latter case may become confluent. As they increase in size they undergo central caseation and softening, and appear as opaque yellowish nodules elevated above the surface of the mucosa. As the caseation increases the overlying mucosa becomes involved and the caseous material is liberated into the intestinal lumen, leaving a small round, punched-out cavity in the centre of the milary nodules. With the extension of the process these caseous cavities become larger and take on the character of ulcers having more or less ragged, often undermined, edges surrounded by an elevated border in which grayish translucent, or yellowish opaque milary nodules are usually present. The floor of the ulcer is covered with caseous material and may also be set with milary tubercles. The process is usually shallow in the majority of cases, but the caseation and subsequent erosion may extend to any depth in the intestinal wall, not infrequently into the muscle-coats. Rapidly developing tuberculous ulcers may lead to perforation, either into the peritoneal cavity or into a neighboring coil of intestine in case adhesions have formed. More often there is a local peritonitis leading to the formation of adhesions or local thickenings of the peritoneum preventing perforation into the general peritoneal cavity. Perforation into or between such adhesions may lead to the formation of faecal abscesses. Very rarely perforation into the bladder or uterus or through the abdominal wall may occur.

In the more slowly growing ulcers there is usually an abundant formation of tuberculous granulation tissue in the base of the ulcer or about its edges. This tissue may be so abundantly produced as to cause marked thickening of the wall of the intestine and a constriction of the lumen. Caseous foci are usually present throughout the granulation tissue. Although an entire Peyer's patch may become involved in the ulcer, the long axis of the latter is usually transverse so that "ring" or "girdle ulcers" encircling the intestine are produced. The tuberculous process extends along the lymphatics of the intestinal wall, and a tuberculous lymphangitis is practically always present in the immediate neighborhood of the ulcer. The involved lymph-vessels appear to the naked eye as tortuous whitish beaded lines or cords. Milary tubercles may be found along the course of the affected vessels. The resulting chyle stasis leads to general or local dilatations of the lymphatics, in the latter case appearing as chyle cysts. Milary nodules occur in the subserosa near the ulcer, and the site of the intestinal ulcer can be told by the local peritonitis and lymphangitis, and the mesenteric glands are always involved in such cases. In many cases tuberculous lesions are found also in the thoracic duct. From these the bacilli may be given off into the lymph and thence into the blood stream in such numbers that a general milary tuberculosis is produced. Moreover, tubercle bacilli may pass into the thoracic duct from the intestinal lesion or the caseous mesenteric glands, and reach the blood-stream without exciting any lesions in the duct itself. The importance of intestinal tuberculosis in the production of reinfections and widespread metastases is very evident.

Small isolated tuberculous ulcers in a state of repair may occasionally be found in the intestinal wall, particularly in patients dying during the early stages of a pulmonary tuberculosis. Regeneration of the mucosa to a greater or less degree is often found about the edges of the more chronic ulcers. The new-forming epithelium pushes in from the sides and overhangs the floor of the ulcer, often forming polypoid growths. Contraction of the ulcer during the healing process may lead to a stenosis of the intestinal lumen. The mucosa of the intestine in the neighborhood of the tuberculous lesions presents the picture of a subacute or chronic catarrhal inflammation, or more rarely that of a diphtheritic enteritis or colitis. Diarrhoea is usually present in the advanced cases, and this symptom is the

result of the diffuse inflammatory changes in the mucosa.

In advanced progressive cases the lesions in the ileum increase in size and severity toward the ileo-caecal valve. Through the confluence of the ulcers a large portion of the mucosa may be destroyed. In addition to the larger ulcers hundreds of small tuberculous erosions may be found over milary tubercles scattered throughout the mucosa or located in the solitary follicles. The small-intestine aspect of the ileo-caecal valve usually presents the most marked ulceration. In the *colon* the ulcers are rarely ring-shaped, but are usually round or irregular, and more shallow than those in the ileum. In many cases they are more numerous in the caecum and ascending colon, and diminish in number in the transverse and descending colon to become more numerous again in the *rectum*. The tuberculous process in the mucosa of the rectum is often associated with the formation of perirectal tubercles leading to the formation of fistulous tracts opening in or about the anus. The entire rectal mucosa may become ulcerated or greatly thickened from the formation of tuberculous granulation tissue. Numerous false passages may be formed. Polypoid growths may develop, or a stricture may result.

The *appendix* may be involved in the advanced cases, the pathological picture being the same as that seen in the large intestine. Milary tubercles may be found in the mucosa or submucosa, or the mucosa may contain tuberculous ulcers. Occasionally the entire appendix is converted into a sac filled with caseous material. The appendix may also contain secondary milary tubercles in cases of primary tuberculosis of the Fallopian tubes, the remaining portion of the intestine showing no lesions. *Primary appendical tuberculosis* is rare. The pathological picture is the same as that seen in the secondary form.

Hyperplastic Variety of Intestinal Tuberculosis.—A rare form of intestinal tuberculosis is that associated with a marked thickening of the intestinal wall due to the formation of tubercles in the submucosa and muscularis. The overlying mucosa may show no change beyond that of atrophy. Ulceration may be entirely absent. There is little or no caseation. The ileo-caecal region is usually affected, although the process may involve any coils that become adherent to the seat of the primary lesion. Strictures of the intestine may be produced at intervals, while the intervening portions of the intestine may be relatively normal or show a much less advanced stage of the disease. In the neighborhood of the constrictions the peritoneum is usually studded with pedunculated masses of tubercles, and the neighboring mesentery is thickened and infiltrated with tuberculous granulation tissue. The corresponding mesenteric glands are tuberculous. Polypoid masses of tubercle may also project into the lumen of the bowel. These may be covered with mucosa, either normal or atrophic, but rarely showing ulceration. In some cases typical tubercles are not formed; the tissues are found to be infiltrated with round cells without epithelioid cells or caseation, although tubercle bacilli can be demonstrated in great numbers between the cells of the infiltration. The condition of hyperplastic intestinal tuberculosis is usually primary; only rarely is it accompanied by pulmonary disease. In the later stages of the disease the infection may become generalized, and death usually results from such complications. The slow development of the disease and its peculiar pathology point to an infection with a strain of tubercle bacillus of relatively low virulence.

SYMPTOMS.—The symptoms of intestinal tuberculosis, whether primary or secondary, are often vague. Diarrhoea and constipation may alternate, or either one of these symptoms may be the predominant feature. Colicky pains may be present, occurring mostly in the lower part of the abdomen. These may be transient and of a slight degree, or severe and persistent. The pain is usually more severe after eating or preceding

bowel movements. Nausea and vomiting may accompany the pain. In many cases a marked thirst is present. Blood in the stools visible to the naked eye is rare, but the occult test may reveal its presence in the ulcerative forms. Tubercle bacilli may be found in the stools, but as the presence of the bacilli in the faeces may be due to the swallowing of sputum containing them, their presence cannot be taken as a positive sign of intestinal involvement. In the more advanced cases a chronic diarrhoea is usually present. The symptoms of secondary intestinal tuberculosis are often entirely obscured by the severity of the primary pulmonary affection. The presence of the intestinal involvement may be revealed only through the occurrence of a severe hemorrhage from the bowels, or the symptoms of a stenosis. The symptoms of a *tuberculous appendicitis* are also very vague, and the condition has usually been discovered only at autopsy. The writer has seen two cases in which the appendix removed for symptoms of appendicitis showed the presence of tubercles in the absence of symptoms of tuberculosis elsewhere in the body. In rectal tuberculosis the chief symptom is the pain, which may be constant or intermittent. It is increased by defecation. Symptoms of rectal stenosis may develop in rare cases.

In the absence of symptoms of tuberculosis elsewhere in the body the clinical complex of loss of weight, fever, night-sweats, etc., in connection with alternating diarrhoea and constipation, abdominal pain, etc., would indicate a primary intestinal tuberculosis.

The symptoms of the *hypertrophic form* are also vague. Loss of weight, weakness, abdominal pains with crises corresponding to temporary obstruction of the intestinal lumen at the points of stricture, alternating diarrhoea and constipation, nausea and vomiting, slowly developing abdominal tumor, etc., point to the existence of a hypertrophic intestinal tuberculosis. Fever is usually absent in this form; and characteristic painful points are not present. Distention of the abdomen is rare. The tumors are usually multiple, often cylindrical in shape, and are more or less movable. They are tender on deep palpation, and show a progressive increase in size. In the cases with well-marked stenoses characteristic gurgling borborygmi may often be heard at the end of the colicky attacks as the result of the passage of gas and fluids through the stenosis. As the degree of stenosis increases, the symptoms of obstruction become more pronounced and the characteristic vomiting of this condition may then occur. In the early stages the vomiting is not suggestive of either obstruction, appendicitis, or peritonitis. The general picture may suggest the existence of malignant intestinal disease, and the condition is sometimes mistaken for the latter, even at operation. Hyperplastic tuberculosis of the intestine is, however, seen most frequently in early adult life.

DIAGNOSIS.—The diagnosis of primary tuberculosis of the intestines of the ulcerative type rests upon the occurrence of diarrhoea alternating with constipation, or a chronic diarrhoea associated with abdominal pain, emaciation, night-sweats, fever, etc. The tuberculin test may be employed in doubtful cases, or the opsonic index taken on several successive days may serve as a factor in the diagnosis. The stools should be examined for tubercle bacilli according to the method of Strassburger. They are diluted and sedimented first with water and then with alcohol, thereby decreasing the specific gravity and hastening sedimentation. The final sediment thus obtained may be utilized for making smears that are to be stained in the usual way.

In the differential diagnosis of primary hypertrophic tuberculosis of the intestine the presence of a tumor or tumors showing progressive enlargement, without generalized distention, fever, or leucocytosis would serve to differentiate this condition from appendicitis. In the differentiation from malignant disease of some one of the abdominal organs the tuberculin test, Calmette's reaction, the opsonic index, etc., may be used as diagnos-

tic aids. Exploratory operation may ultimately be indicated.

The diagnosis of secondary intestinal tuberculosis is often difficult or impossible, since the intestinal condition may be masked by the more severe general symptoms. Intestinal involvement may safely be assumed to exist in practically every case of advanced pulmonary tuberculosis. Symptoms of enteritis usually indicate its existence.

PROGNOSIS.—Undoubtedly patients with primary tuberculosis of the intestine may recover. There is good reason to believe that small lesions at the point of entrance of the bacilli in the intestinal mucosa may entirely disappear. Secondary lesions sometimes heal, but as the majority of these occur in advanced cases of pulmonary disease the prognosis is usually hopeless. In the case of the hypertrophic form early operation may effect a cure; but at the stage in which the affection is usually recognized and operated upon generalization of the infection usually occurs after one or more years.

TREATMENT.—The medical treatment of intestinal tuberculosis is almost wholly symptomatic, and usually without much effect. The regulation of the diet is the most important factor in checking the symptoms of enteritis. Fruits, vegetables, etc., are to be prohibited. In very severe cases it may be necessary to resort to the use of boiled milk or albumin water. Lime water may be used with the milk. The general treatment is that accorded late stages of pulmonary tuberculosis.

Local applications, ice- or hot-water bag, turpentine stupes, etc., may serve to relieve the abdominal pain in those cases in which this is a serious symptom. Irrigation with salt solution to which a few drops of laudanum have been added is recommended. Enemata of starch and laudanum, or suppositories of opium or morphine, become necessary in the great majority of cases.

In the case of primary intestinal tuberculosis, particularly of the hyperplastic type, the excision of the affected portion of the bowel offers a hope of recovery in those patients in whom an early diagnosis is made. The ileocaecal portion of the gut may be resected and the local lymph-nodes removed. The after-treatment should be that directed against tuberculous infection in general. When excision is impossible a lateral anastomosis may effect great relief. The treatment of tuberculous appendicitis, perirectal abscess, fistula-in-ano, etc., becomes ultimately surgical, although the usual symptomatic medical measures may be used according to indications. Excision of the abscess or fistulous tract may result in complete healing. A similar result has also followed the injection of mercurial ointment.

Alfred Scott Warthin.

IOTHION is the diiodohydroxypropane, $C_3H_5I_2(OH)$. It is a thick, yellowish, oily, heavy liquid of a peculiar odor, neutral reaction, containing eighty per cent. of iodine. Sparingly soluble in water, easily so in alcohol, ether, and fatty oils and lanolin or adeps lanæ. Applied to the skin it is quickly absorbed, iodine reaction showing in the urine in an hour after taking. This property of absorption allows of the iodine coming in immediate contact with the diseased tissues, thus avoiding the gastric disturbances which follow the iodine when given internally; besides, the general organism does not suffer from the potassium or other content of chemicals commonly used to influence local lesions.

The drug is used in tertiary syphilis and other diseases affecting the skin, mucous membrane, and bones, also in late secondary types of syphilis in combination with mercurial injections; in periostitis, inflammation of the joints, and enlargements of the glands.

Iothion may be applied pure with a brush to the unbroken or uninfamed skin, or diluted with oil twenty-five per cent.; solution in alcohol or glycerin fifty per cent.; or in ointments with lanolin or vaseline, or a mixture of the two, in twenty-five to fifty per cent. strength. When applied to the mucous membrane or sensitive regions it should be used with care, as it may produce irritation.

John W. Wainwright.

IRON, POISONING BY.—Metallic iron and those compounds of iron which are insoluble in water are not poisons. The soluble salts, however, though not active poisons, have an irritant action, and are capable of destroying life when taken in large doses and in a concentrated state. The continued administration of medicinal doses even produces, after a time, decided gastric disturbance. It is probable that all the soluble preparations may act as irritant poisons when administered in large doses. The most important, however, from a medico-legal point of view, are ferrous sulphate (copperas, green vitriol), ferric chloride (perchloride), which is used medicinally in the form of tincture, and the tannate in the form of ink.

The salts of iron are rarely administered for criminal purposes. Most of the reported cases of poisoning have been the result of accident, or of the use of the sulphate or the tincture of the chloride of iron in attempts at abortion. The symptoms which follow the administration of large doses of the preparations named are essentially similar to those produced by the irritants in general. There are a styptic taste in the mouth, nausea, vomiting, pain in the stomach and intestines, and purging. The evacuations are black, owing to the conversion of the iron salt into a tannate by the tannic acid of the food, or into a sulphide by the sulphureted hydrogen resulting from decomposition in the intestines. Irritation of the genito-urinary passages is sometimes observed. The tincture of the chloride of iron is more corrosive in its action than the sulphate, by reason, apparently, of the free hydrochloric acid which it frequently contains. Its injection into the cavities of the body, for the purpose of arresting hemorrhage, has proved fatal.

The amount of any of the preparations of iron required to endanger life is not accurately known, but appears to be quite large. In most of the cases in which the sulphate has been taken, the amount was unknown. Recovery has taken place after a dose of 31 gm. ($\frac{3}{4}$ i.) of the sulphate (Christison). A case is reported in which 48 gm. (fl $\frac{3}{4}$ iss.) of the tincture of the chloride of iron proved fatal in about five weeks (Christison). Recovery has taken place after doses of 32-96 gm. of this preparation. The favorable issue is probably due, in many cases, to the early occurrence of vomiting.

The results of experiments on animals are not uniform. Gmelin states that 7.7 gm. ($\frac{3}{4}$ ij.) of the sulphate of iron administered to dogs by the mouth caused vomiting only; that 2.6 gm. (gr. xl.) administered to rabbits produced no injury; and that 1.3 gm. (gr. xx.) injected into the veins of a dog produced no symptom whatever. Dr. Smith, however, states that 7.7 gm. will prove fatal to dogs when administered by the mouth or applied to a wound.

The post-mortem appearances are those of a simple irritant, and are confined, so far as has been observed, to the stomach and upper part of the intestines. In acute cases the contents of the intestines will probably present a black appearance, owing to the presence of the tannate or the sulphide of iron.

Iron is eliminated to some extent in the urine. A small amount only is absorbed in any event, the greater part escaping in an insoluble form with the feces.

Treatment consists in the use of the stomach-pump, or of emetics if necessary. Magnesia or dilute solutions of alkaline carbonates should be administered as antidotes, and these should be followed by demulcents.

William B. Hills.

LA BOURBOULE.—La Bourboule is situated in the central portion of France, directly south from Paris, from which it is distant 282 miles, about ten hours' ride by rail. It is famous for its hot arsenical springs. La Bourboule lies in a valley of the Auvergne Mountains, at an elevation of 2,700 feet. It is open to the east and south, but protected on the north and west by the mountains. The climate possesses the characteristics of that of medium altitudes; it is tonic, sunny, and invigorating. Thunder-storms of short duration are frequent, as in other mountain resorts. The scenery is

varied and attractive, and there are many interesting excursions in the neighborhood. The season extends from May 25th to October 30th.

The fame of these waters depends upon the arsenic they contain, being the richest hot arsenical waters known. They also contain in very considerable amounts bicarbonate and chloride of sodium. They are employed in diseases for which arsenic is applicable and beneficial. There are also cold springs, but the hot ones are chiefly if not exclusively employed.

The two hot springs are "La Source Choussy-Perrière," of a temperature of 136° F., containing in a litre 3 gm. of sodium chloride, 3.8 of sodium bicarbonate, and 0.028 of sodium arsenate; and "La Source Croizat," of a temperature of 113° F., containing 5.63 gm. of sodium chloride, 3.0 of sodium bicarbonate, and 0.025 of arseniate of sodium. The water is clear, with a salt taste and without odor. It is used for drinking, baths, and inhalation; the internal use of the water is the most important, and it is drunk at about a temperature of 100° F. in daily doses of from three to eighteen ounces, or even more, divided into three portions, taken at different times of the day.

The baths are taken separately or in a common pool, and in skin affections they are often prolonged for several hours, but the water is not very hot. In the inhalation chambers the water is finely pulverized, and thus employed in respiratory affections. Pulverization chambers with numerous apparatus for nasopharyngeal and cutaneous affections, and various kinds of douches, vapor baths, arrangements for dry and wet massage, are all found in the well-equipped bath establishment.

The diseases for which these waters are applicable and beneficial are: first, chronic skin diseases, such as eczema, ichthyosis, psoriasis, lichen ruber, lupus, urticaria, etc.; second, chronic diseases of children, such as glandular enlargements, scrofula, tuberculous diseases of the bones—weakly children and those with a tuberculous inheritance, and, as well, those with whom the seaside disagrees, are also benefited by these waters and the climate; third, anæmia and chlorosis, when not amenable to the iron treatment; fourth, chronic catarrhal conditions of the pharynx, larynx, trachea, and bronchi, when there is an arthritic or neuroarthritic tendency, especially when associated with a skin affection; fifth, malarial cachexia, neurasthenia with anæmia, certain cases of arthritis deformans, neuralgia resulting from malaria, the cachexia of syphilis, feeble, rheumatic, and gouty persons; sixth, diabetes and some forms of albuminuria.

Contraindications: Those conditions for which the water-cure treatment in general is contraindicated,—advanced arteriosclerosis, degeneration of the myocardium, degenerative changes in the cerebral arteries, non-compensated valvular diseases of the heart, malignant diseases, extreme age, fever, and, in particular, a hemorrhagic tendency, cirrhosis of the liver, and renal lithiasis.

The duration of the "cure" is generally very short, varying according to the malady and the results obtained.

The accommodations are abundant and good. Four thousand persons, it is said, can be received at one time, and, as has been said, the bath establishments are well equipped and elaborate. There are the usual amusements found at French watering-places,—music, theatre, casino, parks, and promenades. Here, as at all well-known spas, reliable medical advice can be obtained.

The La Bourboule waters are exported and can be obtained in any country. *Edward O. Otis.*

LEUKÆMIA.—**TREATMENT BY ROENTGEN IRRADIATION.**—The application of the Roentgen rays to the treatment of leukæmia was first made by American physicians, Pusey (1902), Senn (1903), and Brown, Bryant, and Crane (1904). The results obtained by the treatment were so striking that the attention of the entire medical world was directed to the method, and it was at once given a trial wherever leukæmic patients were accessible.

Since 1904 more than two hundred cases of leukæmia have been reported in the literature as having been treated by Roentgen irradiation, and it is now possible to draw certain conclusions concerning the value of the treatment, and the following statements are based upon an analysis of the reported cases.

As the result of the repeated exposures of short duration there occurs in many cases of myelæmia a symptomatic cure, manifesting itself by a marked reduction in the size of the spleen and in a great improvement or return to the normal of the blood condition. The number of the white cells may be brought back to normal, the red-cell count increased, and the color index raised. In some cases the relative proportion of the white cells appears also to be restored to the normal; but in the cases most carefully studied the blood still shows leukæmic characteristics in the presence of myelocytes, mast-cells, or atypical white cells. Nevertheless the number of these cells is often reduced from high proportions to such low ones that on a superficial examination the white cells may appear to be in normal variety and proportion. The general condition of the patient is greatly improved, and he is often enabled to return to his business or occupation, and for a number of months he may show such a freedom from symptoms that he may regard himself as cured.

Such a cure is, however, only a *symptomatic* one; sooner or later recurrence takes place and the disease goes its usual course to a fatal end. No proof of an absolute cure of myelæmia by Roentgen irradiation has yet been produced. Moreover, not all cases of myelæmia respond to the treatment, even when the irradiation is continued for some time. Those cases of myelæmia presenting the symptom of pain in the bones or enlarged lymph glands react to the treatment very slowly, or may not respond to it at all. Occasional cases in which these symptoms are not present also fail wholly to react favorably to the treatment with Roentgen rays, even when it is extended over some period of time.

Cases of lymphæmia are influenced by irradiation to a much less degree than those of myelæmia. Nevertheless in some cases the number of the white cells is reduced, and the spleen and lymph glands diminished in size. The erythrocyte count and the color index are likewise raised, but the relative proportion of the different forms of white cells is not, as a rule, greatly affected. Only in a few cases is the normal proportion restored. Occasionally the proportion of the lymphocytes rises during the treatment; and an aleukæmic lymphocytoma may be transformed into a lymphatic leukæmia during the course of treatment by Roentgen irradiation. The reports in the literature do not show such a uniformity of results in the treatment of lymphatic leukæmia as in the case of myelæmia, therefore such definite statements cannot be made concerning the former. In general the cases of lymphatic leukæmia require a much more vigorous and protracted treatment with the rays in order to bring about approximately the same results as may be obtained in myelæmia. In those cases of lymphæmia in which there is an improvement of the blood condition the general state of the patient is likewise bettered.

In the case of both myelæmia and lymphæmia the earlier the treatment is begun the more marked is the reaction. This apparently does not apply to the condition diagnosed clinically as "acute leukæmia," since in this form the treatment by irradiation does not appear to give good results. Moreover, in a few cases of chronic myelæmia the treatment has apparently produced an exacerbation of the symptoms with the clinical appearances of an acute intoxication terminating speedily in death. Inasmuch as such phenomena may occur in cases of leukæmia not treated by Roentgen irradiation they cannot definitely be ascribed to the treatment.

Nevertheless certain dangers are associated with the use of Roentgen rays as a therapeutic agent in the treatment of leukæmia. Aside from the local effects upon the skin ("x-ray burn") and the changes produced in

the sexual glands (sterility), that can to a large extent be guarded against by proper technique, there are certain specific dangers attending the treatment that must be considered. These dangers are the direct outcome of the changes produced in the body by the rays, and it is in these very changes that the good results of the treatment lie. The researches of Heineke, Warthin, and others have shown the selective destructive action of Roentgen rays upon the lymphocytes and myelocytes, and their parent cells in the spleen, lymph glands, and bone-marrow. To such a destruction of white cells and their parent cells is the improvement seen in leukæmia due. It has also been shown that this destruction goes on for some time after irradiation; in some cases the diminution in the number of white cells has persisted for weeks after the treatment has ceased. Such a persistent leucocytolysis has been explained on the ground of a formation of a "leucotoxin," and a number of writers (Curschmann and Gaupp, Schmidt and Geronne, Capps, etc.) believe that they have demonstrated the presence of such a leucotoxin in the blood of cases of leukæmia treated by irradiation. According to Schmidt and Geronne the leucotoxin is excreted by the kidneys, since in nephrectomized animals the leucocytolysis following irradiation is much greater than in normal animals.

The disintegration of such a large amount of nucleoprotein in the body with the resulting severe disturbance of metabolism that must occur in the case of the destruction of great numbers of white cells by the rays would favor the occurrence of a toxæmia. That such a metabolic disturbance occurs is shown by the increased total nitrogen output in the urine, with an increase in the excretion of uric acid, purin bases, and phosphates. Clinical evidence of such an intoxication is shown in the rapidly developing toxic conditions sometimes seen after one irradiation only. The typhoidal state, fever, nervous phenomena, etc., all suggest an intoxication of proteid origin. In some cases these symptoms lead quickly to death. Experimental investigations also favor this view of the nature of the toxic reaction produced by the Roentgen rays.

A second danger lies in the production of kidney changes through the excretion of toxic substances. Warthin has shown that the kidneys of five cases of leukæmia treated for some time with Roentgen irradiation presented marked degenerative changes with extensive deposits of lime salts, resembling the changes sometimes seen after poisoning with mercuric chloride, etc. Experimental investigations have shown also that renal changes may be produced by repeated or prolonged irradiation of the body. Schmidt and Geronne believe that the leucotoxin developing after Roentgen irradiation is excreted through the kidneys, and it is possible that this poison may also affect the renal epithelium.

In spite of these dangers the analysis of the cases reported up to the present time justifies the use of Roentgen irradiation through the fact that in many cases it causes a marked though temporary improvement, and prolongs the patient's life for a definite period of time. Inasmuch as leukæmia is a hopeless disease, leading to a fatal termination in a relatively short time, any method by which the final event can be postponed is certainly a therapeutic gain. Practically the only other method by which the course of leukæmia can be altered is by the internal administration of arsenic. This drug must, however, be pushed to its physiological limits, so that the danger of arsenical poisoning must always be considered. The degree of leucocytolysis following the administration of arsenic is less than that following irradiation, and the white-cell count rises more quickly afterward. The persistent leucocytolysis seen often after but a few exposures to the rays does not find a parallel in the case of arsenic; and the reduction in the size of the spleen and lymph glands is always more marked in the case of Roentgen irradiation. Moreover, a relatively large number of patients do not react favorably to the

arsenic treatment. Symptoms of proteid intoxication may also occur suddenly during the course of treatment with arsenic, so that this phenomenon cannot be regarded as a direct sequel of either form of treatment.

Taking everything into consideration, we must regard the treatment by irradiation as the one offering to the patient the greatest number of chances for a temporary symptomatic cure, whereby he may secure a respite of weeks or months. To business men such a postponement of the fatal termination may be a matter of great moment.

Since both the Roentgen rays and arsenic have the common property of causing leucocytolysis, and as the continued use of either one is attended by certain dangers, the most rational plan of treatment would appear to be an alternation of the two. This has been advised by a number of writers who have found by experience that the coincident use of the two therapeutic agents, with alternation according to indications, leads to the most marked improvement.

The treatment of the leukæmic patient by irradiation should be placed in the hands of an expert operator. Thorough protection against the incidental dangers of the exposures should be afforded; all portions of the body of the patient except that to be treated should be protected. A medium tube is advised by those who have had the best results; and short exposures are given for a definite period, and then the irradiation is omitted for a time while the internal administration of arsenic is pushed. The periods between the Roentgen-ray treatments should be gradually lengthened. In cases of myelæmia the spleen and the long bones are alternately exposed. As the spleen is more easily influenced by the rays this organ should be more frequently exposed than the bones. When the lymph glands are enlarged these should also be treated in turn. In cases of lymphatic leukæmia the spleen, regional lymph glands, and bones are exposed alternately.

During the course of the treatment it is very important for the physician to control the exposures by making thorough examinations of the patient's blood and urine. An increase in the number of white cells during the periods between the exposures is an indication for renewing the latter. It must be borne in mind, however, that the first exposures often cause in leukæmic cases first a rise in the number of white cells and then a fall, while after repeated exposures this primary increase does not occur and the fall takes place at once. A decrease in the number of red cells should be taken as an indication for pushing the arsenic. The changes in the spleen and lymph glands may also be taken as a guide to the treatment. The urine examination should include an estimation from time to time of the total nitrogen output. A very great increase in this should warn against the possibility of an impending toxæmia or general disturbance of metabolism. Further, the urine examination should guard against the production of a toxic nephritis or against an exacerbation of a previously existing renal condition. *Aldred Scott Warthin.*

LIGHT: ITS PHYSICS, PHYSIOLOGY, AND THERAPY.—There is a fundamental difference in the action on living protoplasm of the infrared rays of the sun and the ultraviolet. The former are called thermic because their chief effect is to increase the molecular movements constituting heat, while the latter are called actinic, because they destroy chemical compounds by causing atomic movements within the molecule. Matter being at rest only at the absolute zero, the molecules of every substance are perpetually vibrating at various rates and with an intensity of movement corresponding to the temperature. Every kind of protoplasm has a range of temperature within which it can function. Below the minimum its "vitality" is suspended, as its molecular movements are too slow or restricted, and if it is kept cold it eventually dies. If its temperature is raised above the maximum, the molecules vibrate too rapidly and the action is pathological, and if the tem-

perature is still higher the chemical constitution is changed and death occurs. The higher animals by oxidation of food are able to produce enough heat to keep their living cells at the proper temperature, but this ability is far less in the lower forms. In the lowest and in plants the cells are wholly dependent upon the heat derived from the sun, although every living cell, animal or plant, does produce some heat as it consumes oxygen and excretes carbonic oxide. The leaf cells are merely food gatherers, absorbing light, and by means of this actinic energy they break up the carbonic oxide of the air, but the living cells under the bark, or in the roots and buds, act like animal cells and respire the same.

The whole living world is thus dependent upon the sun's heat for proper temperature, and its light is the ultimate source of all food, facts which have completely hidden from us the knowledge of the actinic effects of light and ultraviolet rays. It is known that these waves are entirely too rapid to cause movements of the huge bulky molecule of protoplasm, consisting of groups of atoms which according to some physicist might amount to hundreds of thousands. In passing it might be said that the latest descriptions of the ether by physicists show that the enormous elasticity required to transmit such rapid waves at tremendous speed presumes an almost inconceivable rigidity, and that radiant light and heat are perhaps not vibrations, but are of the nature of rapidly alternating stresses or strains. But their effect upon matter is to cause actual movements of molecules, or the atoms composing the molecule, or the corpuscles composing the atom, and for our purpose we may call them vibrations, waves, or rays. The octave, red to violet, besides the power to affect the retina, produces both molecular or thermic and actinic or atomic effects, but the thermic power rapidly diminishes from the red end, and the actinic from the violet. Red light is too slow to cause much disturbance inside the molecule, and the violet is too rapid to cause much movement of the molecule as a whole.

There is an invariable biological law, without a single known exception: living cells are so placed that they can receive sufficient thermic vibrations and be protected from excessive actinic ones. All plant cells function in the dark, under the bark of the roots, trunk, and branches. Even the carbon-gathering leaf cells are not an exception, for they are guarded by the green chlorophyll, and if that is insufficient they are protected by hairs and thick skin, or they turn the leaf edges to the light, migrate from the surface, or get protection in some other way. Most animals pass their lives in the dark of the deep sea or in the soil, and the few species which come out from lairs in the daytime are covered with hair, feathers, or pigment, and all exposed surfaces are pigmented. Unpigmented ants and grubs promptly die in the light.

Man himself obeys the same law, for each type is pigmented in direct proportion to the amount of light to which it is exposed in its ancestral home, irrespective of the heat or cold, for the glare of the arctic snow requires almost as much pigment as the direct rays of the subtropics. Indeed, by the laws of absorption and radiation of dark heat, pigment is really a disadvantage in high external heat, for it absorbs well, and black tropical animals, including the black man, tend to hide from the midday sun, while the white tropical birds endure, for the white feathers are opaque to light but reflect and radiate heat. Blondness is an advantage in dark external heat above 98.6°, for it does not absorb well, and white men have been known to stand such heat, as in fire-rooms, which prostrated negroes, but blondness is a fatal disadvantage in ordinary tropical heat less than 98.6°, for it then radiates less, and white men are feverish where negroes are normal. In the matter of tropical clothing, white is the best for its reflection, but at night or indoors black is coolest, as it radiates best. In cold climates black is warmest in the day as it absorbs the sun's heat, but white is warmest

at night, as it radiates heat, and arctic animals dress in white in their long night.

Blondness is then a tremendous advantage in cold dark countries, for it radiates less, and such men require less clothing than negroes in temperate zones. We find that the cold cloudy southern third of Norway is the centre of blondness of the world, where there are blonder men and more of them per 100,000 than elsewhere, and on any line drawn from this centre we find the blonds darker and less numerous the further out we follow it. Moreover, migration from this centre is followed by extinction, which comes sooner the further the migration. History is full of illustrations, and the facts are now evident in America, even in Canada, where Houtan in 1690 said that few of the Frenchwomen were brunettes (quoted by Francis Parkman). The increasing brunetness of Americans was noted long before the present flood of brunette immigration. An apparent exception is found among mountaineers who are blonder than the surrounding plains people, but this is due to the lower temperature and greater cloudiness, some mountains being almost perpetually enveloped in clouds, the climate resembling that of Norway. We find blue-eyed people in the mountains of Northern Spain and Italy, though few or none of these are white-skinned, yellow-haired types. In our Appalachian system there are similar conditions, even at its southern extension, where the rainfall is enormous and cloudiness exists throughout the year. Light types can survive there as long as in similar European mountains. On the northwest coast, where the rains and clouds so closely resemble those of Scotland and Norway, we find as a fact that Scotch and Scandinavian yellow-haired types preserve their health and nerves better than in any other part of the United States, and perhaps may survive permanently. To a less extent we may assert the same of the cloudy regions of New England and Canada, but the yellow-haired lines have survived to only a limited extent, the blue-eyed people having brown hair as a rule. The best protected, of course, are those who are as swarthy as the native Indians.

In light countries, then, the blonds should show a greater morbidity and mortality; as that is the only possible way in which types can change in so few generations. It is the law of selection, or the survival of the fittest for survival. Unfortunately there are only a few recorded observations on which we can base accurate generalizations. Until recently anthropologists and physiologists gave little thought to the reasons for the tremendous differences between the races of men, but a "new anthropology" has now been born—a science which is destined to explain these differences. It is the duty of physicians to find out what causes the mortality of types the opposite of what we find surviving, why the very tall have died out here and the very short there, why bulkiness is necessary in one place and slenderness in another, and so on through all the differences. Physicians, as a rule, are not aware that any diseases attack one type more severely than another in any one locality; for such differences, except in the case of white men in the tropics, are small and easily overlooked. It has been found that blonds, even in southern England and in all cities, do suffer from higher mortality and morbidity than brunettes, but, except in certain nervous diseases and tuberculosis, there are no observations and few statistics as to any special diseases. If physicians would record the types of patients, say complexions alone, it would be known exactly how much more liable to tuberculosis are the bright blonds in sunny America than in cloudy Scandinavia. Then we shall prove as to man what botanists and zoologists have long known—that acclimatization is a hopeless impossibility. To survive in the tropics as permanent colonists "white men" should be black.

By keeping in mind the fact that the short waves of the upper spectrum and ultraviolet—and, of course, the still shorter Roentgen rays and the gamma rays of radium—are not able to move the molecule and pro-

duce heat, but are able to move the atom within the molecule, we may form some conception of their pathological results and the rationale of their therapy. A mild application, not sufficient to disturb atomic relations, merely causes increased "vital" action, but as in the case of all stimulations, the ultimate effect is exhaustion. Light baths, for instance, have been proved to cause increased excretion of carbonic oxide, and if they are of excessive intensity, frequency, or duration, there is wasting. Even the farmer knows that he can fatten his stock quicker and cheaper in dark barns than in brilliantly lighted ones.

The preliminary stimulation of white men recently arrived in the tropics is a well-known phenomenon. All the functions—mental, nervous, and physical—are performed with greater ease and energy. Exhaustion comes in time and has received the special name of tropical neurasthenia. To be sure there are many other factors besides light—the heat, for instance—but the fact that blonds suffer more than brunettes in a degree of heat not excessive, and that the same condition is found in the arctic glare, is proof that the light is a large factor, though the fact is not accepted by all tropical experts.

To a lesser degree the same phenomena are found in temperate zones. The stimulation of a bright day after a series of cloudy ones is common knowledge. Many literary men have used sun exposure as a mental stimulant. If there are many brilliant days in the year the effect is multiplied and ultimate exhaustion results. Neurasthenia is thus more common in our sunny climates, and moreover it has been found more often and in worse form in blonds than in brunettes, though of course both types do suffer from it if the other myriad causes are sufficiently intense. Finally, several observers have reported that these patients do remarkably well in sanatoriums situated in cloudy places, but relapse upon return to perpetual sunshine.

It is now known that slight but constantly acting irritations of any sort produce profound effects upon the plastic irritable body, and the constant nagging of intense sunshine upon blonds eventually produces a pitiable state in which each nerve seems to rise on end tingling in protest. There is even a pain, which should be called "sun-pain," for it is relieved by shade, and I have repeatedly so relieved it in nervous women living in tropical houses flooded with intense light. Dr. George M. Gould, of Philadelphia, has proved beyond reasonable doubt that all migraines and occasionally terrible nervous symptoms in every part of the body are sequelæ of the constant strain of the unconscious efforts to obtain acute vision in spite of refractive errors which may be very minute, and the same may be said in minor degree to follow the nagging of light upon bodies insufficiently pigmented. When the two causes are combined the results are deplorable. He has shown that refractive errors are very largely at the basis of that inability to stand the strains of civilization which causes truancy, vagabondage, crime, and worse. My own investigations have shown that among the criminals of New York there is an undue number of blonds, and several observers have reported an undue percentage of blonds among the insane. The foreign-born do not suffer so greatly, but the effect is found in the subsequent generations, so that in some Western prisons, in districts, too, where there is a large foreign element, the criminals are nearly all native-born. In New York the foreign criminals are convicted largely for assaults and other crimes of passion so common in their native lands. The habitual criminals are more commonly natives unable to work and who have thus become social parasites—and these are the ones which show an undue percentage of blonds.

Vagabondage has long been known to be due to a nervous weakness which might be called neurasthenia—a fact which is ignored by all sociologists who have studied our dreadful tramp problem. These idlers are sick men not possessed of enough nerve strength for

constant labor, so that "hard labor" as punishment only increases the trouble. Denmark is the only nation which treats them on scientific grounds. Our "poor white trash" are in the same condition of inefficiency, and some observations here and there in the South have established the fact that they are quite largely of the yellow-haired types on their way to final extinction from the population. Very blond native Americans who are still vigorous are usually offspring from recent immigrants or of the second or third generations unless they come from the old families of the cloudy north or mountains. Even our best athletes are mostly foreign-born or of the second or third generation from Europe. Moreover, they excel in sharp short contests requiring an enormous quick expenditure of energy, but are outclassed by Europeans in feats of endurance, and our national game of baseball requires quickness in expenditure intermitted by long periods of rest. That is, there is a special "nervousness" typical of the United States and British colonies similarly situated, but not found in cloudy rainy climates, and its results are of every grade from unwholesome activity to complete, helplessly incurable neurasthenia. This is one of the reasons European physicians cannot understand American diseases, for there are few places in Europe where there are immigrant types out of their zone.

Blonds, then, in light countries should be less resistant to any infection. The only disease which has received any attention is tuberculosis. We know that there is no harder race than the yellow-haired Scandinavian and Scotch at home, and yet we have been taught that this type is a tuberculous one in sunny America. Recently it has been stated that there is no evidence to support this old idea, yet there are facts in plenty. Statistics at hand show that the blonds of a population furnish a larger percentage of cases than they should, particularly in the cities. There are a few observations to the effect that if the blond patient is not removed to his normal environment, the probability of recovery is less than in the brunette; but as far as now known, he is just as curable as the brunette in cloudy climates like the Adirondacks. The negro is susceptible because he is now living a most unnatural life, but when he was properly fed, clothed, and housed in slavery he was practically immune, so he is not an exception to the rule.

The facts seem destined to compel a radical change in our explanations of other tuberculosis phenomena. For instance, the high mortality of stone-cutters—about forty-five per cent., the highest of any trade or profession—has been said to be due to the inhalation of dust, for they live an out-door life in sunlight, but miners inhale much more dust in their confined galleries, and besides that they live in the dark, which has been considered fatal in itself, yet their mortality is only about seven per cent.—the least of any trade or occupation. Could the excessive sun exposure be the fatal factor in one case, and shade the saving in the other?

Another fact must be kept in mind—the least mortality from tuberculosis is in the cloudiest cities, Berlin, Hamburg, Amsterdam, and London, and the more the sunshine the higher the death rate, the greatest mortality being in Moscow and Naples. Indeed, the whole northwestern cloudy corner of Europe has a less rate than the rest—excepting a little strip running down through the cloudy Alps and Italian mountains.

If light is of greater intensity than that which merely stimulates and exhausts, it so disturbs the molecule as to cause weakness or cessation of vital activity—paresis or paralysis. Locally it thus causes more or less anaesthesia, the greatest effects being said to be obtained from the blue area of the spectrum, and not from the ultraviolet. General anaesthesia has been reported from such application to the eyes, but "suggestion" has not been sufficiently excluded to warrant safe conclusions.

Finally, short rays may cause intramolecular motion of the atoms so violent as to disrupt the chemical com-

bination—the true actinic effect,—and the molecule ceases to be protoplasm and is dead matter. Although protoplasm contains carbon, it is essentially a nitrogen compound, and these are notoriously unstable, some even exploding upon exposure to light. Photography and warfare are based on the instability of such compounds derived from the protoplasm of living cells of past ages. Only recently have we been able to manufacture them from the free nitrogen of the air by electricity. Formerly we depended upon those obtained from mines of organic deposits—saltpetre—or those obtained from ammoniacal decomposition of recently living tissues.

Heat produces results almost instantly—increased activity, paralysis, death, or actual combustion. The effect of short rays is not seen at once, and the shorter the waves, the longer the delay. In the case of radium and x-rays it may be days or weeks before the cells become parietic or die. Some are killed in a few minutes by an amount of light by which others do not seem to be affected at all. Epithelial and atypical cells are destroyed by an application which merely stimulates connective-tissue cells to formation of sclerotic tissues, and this is the basis of much therapy. Youthful, proliferating, lymphoid, and germ cells are also easily killed. The sterilization of x-ray operators is thus caused, and a profound effect also occurs in the whole lymphatic system. Young animals are killed or injured by an application of radium or light more or less harmless to the parents. White men can stand thirty or forty years in the tropics in conditions which are fatal to their children, and the same phenomenon has been reported among blond country-bred city dwellers in both Europe and America.

Nerve cells are specially susceptible, and this fully accounts for the prevalence of the nervous affections above mentioned. Indeed, the hair of the head seems arranged over the superficially situated cerebral cells for this particular purpose, and its wooliness in the tropics, and blackness in all light countries, merely increase the shade. If the hair is removed for comfort indoors, the tropical native instinctively substitutes elaborate head-dresses. The black hats of bald men further north are thus necessary to prevent cerebral damage when out of doors.

The paralyzing and lethal effects of light explain the differences between "heat exhaustion" and "sunstroke," and raise more than a suspicion that the two conditions have been misnamed. Experimental thermic fever is generally of sthenic type, and "sunstrokes" are more common among negro soldiers than white, so that the typical sunstroke with high temperature seems to be due to the molecular heat stimulation. Indeed, I have seen it in a black negro cook working in a ship's galley. The paresis of "heat exhaustion," on the other hand, is what may be expected of light, and it might better be called "light exhaustion." The matter would be cleared up if we had records of complexions to determine whether blonds are more liable to "heat exhaustion" than brunettes. It is known already that the typical thermic "sunstroke" is rare in the Philippines, where the heat is not as intense as in our home cities in summer, while "heat exhaustions" are more common and the light is intense. Nor do "sunstrokes" affect our populations in the sunny West, where it is so easy to keep cool in spite of the high temperature. In the light bath, if the head is not protected, there are symptoms like "heat exhaustion," but they do not appear if the head is protected even if the heat is more intense. Finally, the symptoms are often much delayed in making their appearance—sometimes several hours after the sun exposure—a phenomenon typical of all short-wave applications. As a matter of fact, the majority of cases have been exposed to both heat and light, so that we find every conceivable mixture of symptoms, with and without paresis, fever, or coma, and occasionally chronic neurasthenia follows, as the protoplasm never recuperates. The effects of heat and light are often confused in other conditions.

The paresis due to short rays explains the cancers thus caused. The x-ray fatalities are well known, and Hyde of Chicago has published many facts which leave little doubt that skin cancers are more common in those exposed to excessive light. If an organism is the cause, we are quite sure to be frequently infected in our lives, though the parasite cannot survive in our resisting tissues; but if there is a reduction of vitality due to short rays, senility, or other causes, the germs have full sway. At least this is the most reasonable explanation, as many x-ray injuries of patients are not followed by cancer, while operators are constantly exposed to infection.

The psychic effects of the colors have received a great deal of attention, but the reports are so contradictory that no generalizations can be formed. The only definite statements are to the effect that the red light in photographic dark rooms has caused so much "nervousness" that the operators are now and then disabled unless yellow light is substituted. There is doubt even here, as it seems more reasonable to attribute the results to eye-strain, which must be dreadful in such a dim light, and of course it is relieved in yellow light, which is the most luminous part of the spectrum for the retina. There is no doubt, though, that red does irritate the retina—perhaps a thermic effect. Nurses become very "nervous" during the red-light treatment of the exanthems.

Positive phototherapy according to the desired purpose utilizes one of the three degrees of effect—stimulation, paresis or paralysis, and death—and if the right intensity is not used it does more harm than good. Negative phototherapy, on the other hand, has the opposite purpose of excluding more or less light from cases in which it does harm, and this phase of the subject is as important as the positive.

The value of light baths in stimulating sluggish metabolism is beyond question; even a short stay in the tropics is beneficial in certain forms of rheumatism and "lithæmia," though there has not been an exact differentiation of the cases benefited. The danger exists in over-stimulation and exhaustion, particularly in the senile, who have an undue mortality while visiting the tropics. Locally, in sluggish ulcers, mild light applications have proved quite successful irrespective of the causes, but an excessive amount only makes them worse, as it causes more necrosis.

The parietic effects are mostly useful in causing local anæsthesia for surgical purposes, a field which has been cultivated more in Europe than America. The cessation of pain and discharge in ulcerating epitheliomata is so marked, even in incurable cases, that the method deserves far more use. Unfortunately, if the applications are too mild there is danger of stimulating the growths to greater activity, as in the case of Roentgen rays if too feeble, and the proper dosage has not been worked out to anywhere near the accuracy obtained by the Roentgen-ray operators or by Abbe of New York with radium rays.

The application of strong light for the lethal effects in superficial infections constitutes one of the most brilliant advances in modern medicine. Finsen conceived the idea for the cure of lupus, basing his method on the well-known bactericidal power of the shorter light rays, and he obtained ninety-eight or ninety-nine per cent. of cures even in cases formerly considered hopeless. Since his death it has been found that the rays used are not sufficiently powerful to kill bacilli in a culture medium at the temperature of the tissues, but that the good results are really due to the destruction of the less resistant pathological cells and the stimulation of the more resistant connective tissue, which thereupon replaces the former, the bacilli perishing in the process from some form of antitoxin or phagocytosis. It is amazing that such a brilliant method of cure should have been based on a wrong hypothesis. Moreover, as might have been predicted, it has been found that the most curative are the ultraviolet and the power rapidly diminishes with increasing wave length, being feeble in the blue and

scarcely perceptible from the green down to the red. Finsen really filtered out the ultraviolet by the glass and water of the cooling chamber, and obtained his recoveries by the less efficient violet. There seems also to be a paralysis of the vasomotor nerve endings, for it was found that the rays caused thrombosis and exudation of blood and serum—results long known to be due to ultraviolet rays in glacier burn. Sunburn, too, is known to be mostly due to ultraviolet rays, but here they do not cause blood exudation. Cloudiness, by the way, filters out the ultraviolet, and that is why such days are so soothing.

In other forms of tuberculosis it is now necessary to revise the methods of applying light given for an alleged bactericidal effect. The bacilli are absolutely unharmed in this way, and there is danger of injuring less resistant healthy tissue, increasing metabolism, and causing neurasthenia.

There have been reports of the successful use of concentrated light in quite a number of superficial infections and new growths, chiefly benign, though there are very few operators who produce the ultraviolet, and even if they do, they cut them out by using media opaque to these rays. Consequently there are not many data as to the full extent of their therapeutic usefulness. Roentgen rays and the gamma rays of radium are much shorter, and therefore more efficacious in destroying protoplasm by causing atomic or intramolecular motions. There is scientific ground, then, for the very prevalent impression that better results are obtainable from these than from the ultraviolet. It is an immense field which has scarcely been scratched for cultivation, and it is not yet time to differentiate the respective therapeutic spheres of each of these destructive agents.

Negative phototherapy is as old as the empirical plan of using red curtains in variola. Finsen believed that the light was so irritating that if it was excluded, the pustules would not mature and pitting would be prevented, the disease of itself being insufficient to cause the dreadful results. He was quite convinced that he had obtained excellent results by the method of excluding all light except the non-actinic red, and using only enough of this for vision. In America the results have been uniformly negative, and Finsen thought the failures due to the fact that the light was excluded too late, after the damage had been done, but it is more likely that, as we have more light in America than in cloudy Denmark, we need more complete exclusion. It has been said that our commercial red glass transmits other rays also, and has really admitted actinic rays, but there does seem to be a relation between the severity of the disease and the lightness of a country, and it has also been claimed that Finsen in his cloudy land has been treating a mild form still further modified by vaccination. The damage of light, if any, is very superficial, for the blackest negroes are prone to the disease in its worst form, and their skins keep out most of the light and all the ultraviolet.

In the other exanthems, particularly scarlet fever, there are such frequent references to the great benefits of the negative or red treatment that there does seem to be something to it. Even in superficial suppurations such as impetigo, and in the weeping forms of acute eczema, there are good reports, though sycosis is unaffected. The positive treatment by short rays for the lethal effect on the pathological cells in the skin infections seems to give rise to much more favorable reports.

In neurasthenia the negative treatment has been successfully used a long time; that is, the patient, if a rest case, is kept in darkness during the lightest part of the day. It is far better to send these patients to cloudy climates, such as the mountains or our northwest coast. They are only made worse by intense sunshine, particularly the blonds. The maniacal insane are all made worse by a few days' sunshine, and the practice of forcing them into unshaded bull-pens, exposed to the full glare of the midsummer sun, is dreadful.

I am indebted to Gould for the information that ex-

cessive light increases eye-strain, nature having evolved a dozen or more distinct mechanisms to shade the eyes. Nervous symptoms, for instance, become worse in patients sent to Florida, and oculists are learning that amber-tinted spectacles prevent injury in tropical climes. This fact shows the benefit of excluding some of the rays at each end of the spectrum, both red and violet being irritating to the retina. It is a negative phototherapy more efficacious than the use of smoked glasses, which, by excluding the visual yellows, increase the strain of seeing. Gould suggests amber-colored glasses for blonds in the tropics.

A form of negative treatment in consumption is now receiving wide-spread attention. For instance, in the Adirondacks, where there is a maximum of cloudy days, we find as good results of the modern out-door treatment as in any other part of the world, if not better. It is proof that we have been in error in stating that unstinted sunshine is an essential. A few observers have gone a step further and stated that they have found that the sun-bath invariably raises the temperature, causes prostration, anorexia, and even hemorrhages, so that in the summer the patient must be kept cool and seek the shade. We have also been in error, then, in advising patients to keep in the sun and resist the desire to seek the shade. Moreover, it is found that even bed-ridden patients are always worse in the evening after a day of sunshine, but are in best condition in the morning after a night of darkness. What is still more amazing, the cures are now known to be obtained in the dark winters and not in the light summers. Indeed, many patients grow worse in summer. The old plan of sending them south in the autumn to seek perpetual summer and sunshine thus sends them away from the cold shady conditions which cure them. There is ample reason for the appalling mortality in the tropics and the alleged undue mortality in cold sunny climates, as compared with cold cloudy ones. There are several observers who have mentioned the fact that when sun exposure is tried the blond patients do not improve like the well-protected brunettes; and though this fact has been denied, statistics do show that better results are obtained in the shaded inland sanatoria than on the shadeless seashore, temperature conditions being about the same.

All of these facts show that what is good for one type of man is not necessarily good for the opposite. That is, medical climatology must be studied with anthropology. The best place to send a very blond patient is the climate similar to that in which the blonds are most vigorous, such as southern Scandinavia. The best for the swarthy Mediterranean type is a place like sunny Italy. Acclimatization being impossible, every type is injured more or less by residence in a climate markedly different from the ancestral home, and if we send blonds to sunny lands we do not obtain as good results as if they went to the Adirondacks. Experts now advise white men to wear opaque clothing in the tropics to prevent nervous breakdown, and the tuberculous at home should wear opaque clothes, not translucent ones.

The study of the relative mortality of the various ethnic types in America is a huge field, which is already yielding splendid results bound to modify practice profoundly. The literature as to light alone is so voluminous as to defy references. The most generalized statements alone are possible in the limited space of this article, but more details are found in my work on "The Effect of Tropical Light on White Men," and in a review of the literature in *American Medicine* for April, 1907.

Charles E. Woodruff.

LIPODYSTROPHY, INTESTINAL.—The following case presents an unusual clinical picture and a previously undescribed pathological complex which may be outlined as follows: The clinical picture was characterized by gradual loss of weight and strength over a period of four years, a transient multiple arthritis with pain and swelling of various joints, and a troublesome cough.

The patient was treated for tuberculosis with slight improvement. During the last four months he was troubled with swelling of the abdomen and a slight diarrhoea, three or four stools daily on an average. The stools were creamy in appearance and large in amount. Both fatty-acid crystals and neutral fat were present. No bile was demonstrable. Twenty grams of dried stool contained 10 gm. neutral fat, 6 gm. fatty acids, 4 gm. organic salts, detritus, etc. Blood showed a secondary anaemia (R.B.C. 4,400,000–3,900,000 and hæmoglobin 54–52 per cent.)—a leucocytosis of 7,000–8,500 with an eosinophilia of 3–9 per cent. Urine was negative until shortly before death, when it contained a considerable amount of acetone, but no diacetic acid. This finding is of interest in connection with the manner of death—extreme air hunger resembling that seen in diabetes. The temperature was regularly intermittent with a morning rise to 99°–101°, but there was no reaction to tuberculin, and the sputum examination gave negative results. Physical examination revealed an indefinite resistance or tumor mass below the umbilicus in an abdomen which was rather full and tender. There were fading areas some suggesting purpura, others erythema nodosum. The ankle joints were hot, tender, and swollen, and motion was painful.

The disease in many respects resembled a pulmonary and mesenteric tuberculosis—the cough and fever, progressive emaciation, abdominal swelling, and tenderness, the fatty stools indicating a defective fat absorption but no deficiency in fat splitting. Against this diagnosis were the blood picture—an advanced secondary anaemia with a peculiar eosinophilia—the absence of any reaction to tuberculin, and negative pulmonary signs.

At the autopsy, nineteen hours after death, there were found neutral fat and fatty-acid deposits in the intestinal mucosa, mesenteric and retroperitoneal glands, and thoracic duct; chronic lymphadenitis; anaemia; emaciation; organizing peritonitis, pleuritis, pericarditis, and aortic endocarditis; cardiac dilatation and hypertrophy with fatty degeneration; chronic passive congestion of viscera; splenic tumor; hyperplasia of bone marrow; cloudy swelling of viscera; bronchopneumonia, and oedema of the lungs.

The intestines were dilated. The small intestine showed a pink or red swollen mucosa which was flecked over thickly with little pin-point yellow grains which seemed to be intimately connected with the mucosa, even in some cases just beneath it. No ulceration was present. The Peyer's patches were not conspicuous. The large intestine showed a pale smooth mucosa. The mesenteric glands were greatly enlarged, some of them measuring 3–4 cm. in long diameter, and felt quite elastic. There were many smaller glands close to the mesenteric border averaging 0.5 cm. in diameter. The smaller glands on section were of an opaque yellow color in general, but close inspection revealed a delicate translucent reticulum, between which were grains of a yellow color. Some of the larger glands showed quite extensive hemorrhages into their stroma, but in all glands the small yellow grains were numerous and the feature of interest. The glands about the coeliac axis presented a similar picture. Smears made from these glands showed typical tufts and balls of fatty-acid crystals and a considerable amount of neutral fat, which were present in the intestinal mucosa as well. Microscopically the villi were enlarged, the submucosa thickened, and the mesenteric glands enormously enlarged by deposits of osmic-acid reducing bodies (neutral fats and fatty acids). Such deposits were most striking in the glands, but alike in all these situations. The interglandular stroma contained about the usual number of lymphocytes and plasma cells, but there was an infiltration with great numbers of large mononuclear amoeboid cells with pink granular protoplasm (polyblasts) and many "foamy" cells. The "foamy" cells had an abundant foamy protoplasm, a pale vesicular nucleus, and were actively amoeboid. Ecchymoses were numerous wherever these peculiar cells and the fat deposits were pres-

ent. The submucosa in many places showed these abnormal cells and fat deposits with a definite increase in eosinophiles.

The glands in this affection show the most marked changes. The smaller ones present intact lymph cords and follicles, but an invasion of the sinuses by the peculiar wandering cells and a deposit of small irregular fat droplets. Minute ecchymoses and eosinophiles may be conspicuous. The next stage is an invasion of this tissue by a granulation tissue of fibroblasts and capillaries, an increase in size and number of the fat deposits, and a distortion of the gland architecture. The final stage shows a large gland packed with fat deposits whose stroma is made up of dense fibrous tissue full of ecchymoses and great numbers of giant and mononuclear cells. Gland tissue treated by the Levaditi method shows numbers of a peculiar organism (?) which does not stain by the aniline dyes. These peculiar structures in size and form resemble the tubercle bacillus, but the silver precipitate must cause considerable increase in their size, as in the case of the spirochete of syphilis. They are most numerous in the vicinity of the fat deposits, and are often included in the "foamy" cells. A detailed description of these bodies will be found in the Johns Hopkins Hospital Bulletin, xviii., 198, 1907. Whether they are the active agents in this unusual pathological complex cannot be determined from a study of this single case, but their distribution in the tissues is very suggestive. Cultures and animal inoculations were quite negative.

Chemical study of the mesenteric glands shows both fatty acids and neutral fat to be present in a ratio of 15 to 85 per cent. The fatty acids are derived from the high-melting-point fats. The neutral fats show a low saponification number (144.4), normal saponification numbers being 190 to 208. Lecithin and cholesterolin absent. These findings as well as the microscopical picture support the theory that we are dealing with abnormal fats and fatty acids, or that some toxic substance is held in solution or suspension by them. The finding of acetone in the urine shortly before death, and the extreme air hunger at this time, suggest some acidosis which may be dependent on the disturbance in fat metabolism. The acetone could be accounted for by the starvation of the tissues following obstruction of the mesenteric lymphatics. The large amount of unsplit fat in the stools (one-half by weight) may be explained by the incomplete action of the lipolytic ferment, owing to lack of absorption of its split products. There may be some lack of lipase in the pancreatic secretion, but the gland in the reported case was quite normal in appearance. The peculiar deposits of fat and fatty acids in the tissues may indicate some disturbance in the synthesis of fat which is effected by lipase. These pathological changes are limited to the apparatus which has to do with the absorption of fats, while the lymphatic tissue of the marrow, spleen, bronchial glands, etc., is normal except for changes dependent on a secondary anemia. All these points suggest the possibility that this may be an obscure disease of fat metabolism.

The disease is of some duration, as evidenced by the extreme changes found in the larger glands which show dense scar tissue probably of months' standing. From a comparison with the intestinal lesions it seems probable that the earliest changes took place in the glands rather than in the mucosa, where there is less scar tissue; but the lesions are essentially the same in all locations. The presence of many eosinophile cells in the smaller mesenteric glands probably accounts for the same type of cell found clinically in the blood, and these cells may have some relation to the peculiar structures which appear in the Levaditi sections. G. H. Whipple.

LIPOMA (Adipoma, Steatoma) is a tumor consisting essentially of adipose tissue. Such growths belong to the mature connective-tissue tumors, and have for their

physiological prototype the adipose tissue found beneath the skin and serous membranes. Between normal adipose tissue and the fat tissue of lipomata there are no essential differences of structure. In the majority of lipomata the fat cells as well as the fat lobules are usually larger than those of normal adipose tissue (the former three to four times as large); but this difference does not hold good to such an extent that it can be used as a point in differential diagnosis. In general, a lipoma presents the structural characteristics of a localized mass of fat differing in no respect from normal subcutaneous fat. The chemical reactions of the fat contained in lipomata likewise correspond to those of normal fat.

Since the resemblance in structure to normal adipose tissue is so very close, it may sometimes be difficult to draw a line between a simple hypertrophy of adipose tissue and a lipoma. Both general and local hyperplasias of adipose tissue occur which are not classed with lipomata (general lipomatosis, lipomatous elephantiasis, the deposit of fat about an atrophic kidney or between the bundles of atrophic muscles); but other local hyperplasias of a similar nature have by various authors been styled lipomata. Thus the hyperplasia of the fatty capsule of the mammary gland which occurs sometimes in scirrhus carcinoma of this organ or in chronic interstitial mastitis has been called *lipoma capsulare*, an excessive deposit of fat beneath the epicardium has been styled *lipoma cordis capsulare*, and the deposit of fat in the villous fringes of the joints is known as *lipoma arborescens*, although analogous to the fatty hyperplasia so frequently seen in the epiploic appendages of the large intestine. Such local fatty hyperplasias may be styled *pseudolipomata*. An exact use of the term lipoma would limit its application to those formations of adipose tissue alone in which an actual new formation of fat tissue occurs. Such a criterion has, however, but little practical value, since in the fully developed growth of fat tissue it may be impossible to say whether the latter has arisen from a circumscribed hyperplasia or represents a true neoplasia. This difficulty is increased by the fact that lipomata are usually found in those parts of the body in which there is normally more or less fat tissue. A more practical guide will therefore be found in the principle that the term lipoma should be applied to *circumscribed proliferations of adipose tissue which show a certain anatomical and physiological independence of the neighboring tissue, even when the latter is fat tissue*.

The application of the term lipoma made by some writers to tumors other than connective tissue, the cells of which have undergone fatty degeneration or contain an abundance of fat, is wholly incorrect. The true lipomata belong to the mature connective-tissue tumors—that is, the tissue of which they are composed is of the type of adipose tissue.

HISTOGENESIS.—The histogenesis of lipomata is not yet definitely known. Their very frequent development in regions where fat tissue is normally found has led to the belief that the majority arise from a hyperplastic proliferation of adipose tissue with new formation of fat cells and fat lobules. Such an explanation would hold good even for the lipomata which are sometimes found in the submucosa of the gastro-intestinal tract, since in well-nourished individuals fat cells are usually present in small numbers in this region, and from these a lipoma could take its origin. Another view is that lipomata arise from undifferentiated embryonal cells which have persisted from fetal life, or are formed by the proliferation of connective-tissue cells. The development of fat tissue from these follows the same course as that of the normal development of fat cells from fetal myxomatous tissue. It is not improbable that undifferentiated "primitive fat organs" (developing fat lobules in the fetal mesenchyma) may persist quiescent until adult life and later resume active proliferation, giving rise to localized growths of fat tissue which in their development would be more or less independent of the normal laws of nutrition and cell growth. Support is given to this theory by the fact that some lipomata in their growth appear to be

entirely independent of the laws governing the general nutrition of the body, since they continue to increase in size or at least do not become smaller under conditions of cachexia, etc., when the normal fat tissue is being reduced in amount. The fact that a combination of myxomatous tissue and adipose tissue is frequently found under pathological conditions may also be taken as an indication of the close histogenetic relations of these tissues. In many lipomata areas of myxomatous tissue occur, and occasionally the appearances presented suggest the development of the fat tissue out of the myxomatous. Moreover, there are rare forms of lipomata in which the fat cells resemble those of embryonic adipose tissue, in that the fat droplets are of small size and do not coalesce into larger drops filling the entire cell.

A further origin for lipomata may be found in atrophic lymphadenoid tissue, a physiological paradigm being found in the development of fatty marrow from the lymphoid marrow, and the fatty transformation of the thymus, and later in old age that of the lymphatic glands. The relationship between lymphoid tissue and adipose tissue is very close. In the foetus the development of the lymph glands is either coincident with that of the primitive fat organs or follows it; in the latter case the lymphadenoid structures (both ordinary lymphatic and hæmolymp nodes) developing out of the fat organs. In adult life under certain conditions a new formation of lymph glands takes place from adipose tissue, and in old age the lymph glands become to a large extent replaced by fat tissue. Throughout life it is very probable that there is a constant cycle of alternation between lymphoid tissue and adipose tissue. As the result of some disturbance of these processes it is possible that lipomata may arise, either from atrophic lymph glands or from anlage of undifferentiated cells. Askanazy traces the origin of multiple lipomata in particular to a replacement of lymph glands by fatty tissue.

The lipomata of the uterus, kidney-cortex, brain, spinal cord, etc., are to be referred to misplacements of anlage of fat tissue or of fibrous connective tissue which later undergoes a fatty metaplasia. Such lipomata are to be classed with the heterotopous teratomata. It should be borne in mind also that lipomatous masses not infrequently form the bulk of teratomata found in other regions as well.

ETIOLOGY.—As in the case of the other true neoplasms but little is known of the etiology of lipomata. Some of them may arise as the results of trauma or chronic inflammation. Such an origin has been ascribed to the fatty tumors sometimes found in the hands of working people in the parts most exposed to injury. In other cases fatty tumors have been found developing from scars. The fatty growths in the villi of the joints are usually associated with a chronic arthritis. There also seems to be some association between multiple lipomata and rheumatoid affections. In the case of the multiple and symmetrical lipomata a nervous or trophic origin is assumed by many writers. In such cases other symptoms suggesting a neuropathic origin are not infrequently present. According to Grosch, multiple lipomata of the skin arise from a disturbance of fat secretion by the skin glands due to a trophoneurosis. A connection between lipomata and disease of the thyroid and hypophysis has also been assumed by some authors. In the majority of cases it is very probable that lipomata are to be regarded as congenital, that is, they arise from misplaced anlage. A tendency to the development of lipomata appears also to be inherited in some families.

Gross Appearances.—All lipomata possess a more or less definite capsule. In the sharply circumscribed forms the capsule may be well defined, of varying thickness; in the diffuse forms the capsule is not perfect and often sends prolongations of connective tissue into the surrounding tissues, which if not removed may lead to a recurrence of the growth. The size of lipomata varies greatly; in the kidney, submucosa of the intestinal tract, etc., they may be very small, while in the subcutaneous tissues of the shoulder and back and in the retroperito-

neal tissues they may give rise to tumors weighing fifty pounds or more. As a rule, they do not exceed ten pounds in weight. They usually form lobulated growths of more or less regular contour. A subdivision of the larger lobules into smaller ones gives the growth a tuberculous appearance. Lipomata are not infrequently pedunculated, particularly those found in the submucosa of the alimentary tract, though even in the skin the tumor may occasionally possess a relatively long and narrow pedicle (*lipoma pendulum*). Accessory nodules are rarely seen about the main growth. In the majority of cases lipomata are solitary. Occasionally they are multiple, and in such cases the tumors may be symmetrically distributed over the body. As a rule, lipomata are soft, elastic, and may give a sensation of fluctuation. Puncture with a trocar yields no fluid except in those cases in which extensive retrograde changes have taken place. The absence of fluid on aspiration may therefore have a certain diagnostic value. The occurrence of retrograde changes may render the growth either harder or softer. As a rule, the cut section of a lipoma presents a yellowish or whitish, glistening, lobulated surface, having the characteristic appearances of adipose tissue. In the majority of cases the microscopical examination is hardly necessary for the diagnosis.

Microscopical Appearances.—As stated above, the minute structure of lipomata corresponds in general with that of normal subcutaneous fat. Other varieties of tissue may take part in the make-up of the growth. If the fibrous trabeculae are developed to such an extent that they form a prominent feature of the tumor the latter may be styled a *fibrolipoma*. As the result of the increased consistence of such tumors they are also called *lipoma durum* or *steatoma*. A combination of myxomatous tissue with fatty tissue gives rise to a *myxolipoma*. *Osteolipomata*, *chondrolipomata*, and *myolipomata* have also been described. An abundant blood supply with overdevelopment and dilatation of the blood-vessels gives rise to the form known as *teleangiectatic lipoma*; the formation of blood spaces resembling those of erectile tissue to the variety known as *lipoma cavernosum*. The soft form of fibroma may also be combined with a lipoma. To very cellular varieties of a sarcomatous nature the term *liposarcoma* may be applied. Such forms are rare, sarcoma developing less frequently in lipoma than in any other benign connective-tissue tumor. In rare cases an excessive formation of fat of lipomatous nature may be combined with sarcoma or carcinoma. Lipomatous formations are not uncommon in teratomata, and may form the bulk of the tumor. The presence of other histological elements such as epithelial and nervous tissues gives a basis for differential diagnosis. Varieties of lipomata have also been described in which the fat tissue presented the appearances of embryonic adipose tissue.

Evidences of the growth of the lipoma may be found either in the capsule or in centres of growth which are scattered throughout the tumor. The new formation of adipose tissue may therefore take place peripherally or at different places in the tumor. A fibrous connective tissue is usually first formed, and this later undergoes metaplasia into fat tissue.

Manner of Growth.—According to their manner of development lipomata may be classed as *solitary*, *multiple*, *circumscribed*, *diffuse*, *symmetrical*, etc. The diffuse and multiple forms are closely related on the one hand to the simple hyperplasias of fatty tissue resulting from anomalies of metabolism, overeating, etc.; and, upon the other hand, to the multiple fibromata, chondromata, osteomata, etc., which are congenital or develop from misplaced anlage.

The *diffuse* and *multiple* lipomata, particularly the *symmetrical* forms, have in recent years attracted much attention, and various hypotheses have been advanced in explanation of their origin. In certain cases there appears to be some definite connection between disturbances of the nervous system and the development of multiple lipomata. Numerous clinical observations show the coincidence of occurrence of multiple lipomata and nervous

conditions. The development of symmetrical lipomata in association with disturbances of sensation and motion has been seen in the lower extremities after injury to the spinal column. Neuralgias, trophic disturbances of the skin, etc., have been observed in connection with multiple and symmetrical lipomata. It is probable of course that in some of these cases the nervous disturbances may be the result of pressure by the tumor. Lipomata which are themselves painful are also seen. In such tumors there may be a new formation of nerve fibres, or the tumor may spring from the connective-tissue sheaths of the nerve trunks or the symptoms may be the result of pressure. An exact anatomical distribution of the tumors to accord with the peripheral nerves cannot always be made out. Multiple lipomata may also be inherited. Blaschko reports the case of a family in which the male members developed multiple lipomata at the age of puberty, while the females were not affected. The coincidence of multiple lipomata with rheumatoid affections has already been mentioned.

Broca has reported an extraordinary case of multiple lipomata. In a man of the age of twenty-five years there appeared on the right thigh a small fatty tumor which in six years attained a large size. It was excised, found to weigh five pounds, and to consist of ordinary adipose tissue. The patient remained well for five months when there occurred an eruption of hundreds of small fatty tumors all over the body, fresh ones developing from time to time during a period of forty years. At the age of seventy the man came under Broca's care for treatment for dysphagia. Two thousand and eighty tumors in size from that of a pea to that of a walnut were counted over the body, more minute ones not being included. The original scar showed no signs of disease. The microscopic examination of portions of the growths removed during life gave the appearance of lipofibroma. Increase of dysphagia caused emaciation to set in. This at first did not affect the tumors, but after several weeks the emaciation became extreme and the tumors diminished. The patient finally died of starvation. At autopsy no trace of fat was found in the normal fat depots. A large fatty tumor surrounded the œsophagus for the greater part of its extent, occluding the lumen; the pylorus was surrounded by a similar growth. Fatty growths were found in the valves of the heart, in the deep tissues of the neck, in the sheath of the carotid vessels, and in the sheaths of the muscles, as well as in the normal fat regions. Many of the tumors had lost their fat, they consisted of fibrous tissue; the others presented the appearances of fibrolipomata. It is difficult to explain such a case as this except on the ground of a congenital anomaly.

Site.—Lipomata are found most frequently in those parts of the body where fat tissue is most abundant normally: in the subcutaneous, subserous, and submucous fat, and the intermuscular connective tissue, and less frequently in the kidney, periosteum, joints, tendon sheaths, meninges, etc.

Subcutaneous.—Circumscribed lipomata are found more frequently in the subcutaneous tissues than elsewhere, appearing as movable, lobulated, elastic tumors. The neck, back, gluteal region, thighs, axillæ, anterior abdominal wall, arms, hands, and feet are mentioned in the order of frequency of involvement. Lipomata of the scalp and face are rare. The palms of the hands are more often the seat of fatty tumors than the soles of the feet. In the hands lobules of fat may extend from the main mass of the tumor underneath the palmar fascia. Small lipomata may be found occasionally on the fingers. In regions where the skin is loose the lipoma may become pedunculated. Subcutaneous fatty tumors may reach a very large size. They are sometimes painful and may be associated with nervous symptoms. Ordinarily they are painless. Over the large ones the skin may be stretched to such an extent that it may become very atrophic or may undergo ulceration. In this way the tumor itself may become infected. The loose nature of the fatty tissue and the low resistance of the surrounding

tissue make such an infection dangerous, as it is very likely to become phlegmonous.

The diffuse pseudolipoma of the subcutaneous tissue of the neck may be mentioned here. It is in reality a diffuse fatty hyperplasia and gives rise to the condition known as "fatty collar." The deeper fascia may also be involved, and the lipomatosis may spread over the back, shoulder, and trunk. Similar fatty hyperplasias may occur in the subcutaneous tissue in other parts of the body. In some cases they are symmetrically arranged. In the majority of these cases there seems to be a definite connection between the condition and chronic alcoholism. Under changed conditions the fatty deposits become smaller. The diffuse, multiple, and symmetrical fatty deposits are therefore better classed as pseudolipomata.

Subserous.—Small lipomata are not rare in the subserous tissues. Polypoid fatty growths are occasionally seen in the peritoneum, pericardium, pleura, and the synovial membranes. When possessing a definite pedicle the latter may become twisted and atrophy, or may tear, setting the tumor free into the serous cavity where it appears as a free mass of fat showing more or less calcification. The subserous lipomata may reach a large size, particularly in the retroperitoneal region, and may become dangerous through the pressure exerted upon important organs. Adami has discussed at length the subject of retroperitoneal lipoma, collecting forty cases from the literature and reporting several of his own. As a rule, the fatty tumors of this region are slowly growing, but may attain a very large size. They are usually situated more to one side than to the other, and are usually crossed by some portion of the large intestine. Since they give fluctuation they are generally at first mistaken for cystic tumors, but puncture with the trocar yields no fluid. This fact is the most important point in the differential diagnosis. Small fatty tumors are sometimes seen in connection with femoral and inguinal hernias, but these are more of the nature of local hyperplasias of fat tissue than of true neoplasms. Such hyperplasias may in themselves constitute the hernia, and may drag the intestine down into the sac (hernial lipomata). Similar hyperplasias of the epiploic appendages may present the appearance of pedicled lipomata. Subserous lipomata of the anterior abdominal wall may sometimes appear as subcutaneous tumors as the result of the atrophy or displacement of the abdominal muscles. Large fatty tumors of the omentum have also been reported; in several instances the growth presented the character of a myxolipoma.

Submucous.—Small pedicled lipomata of the gastrointestinal submucosa are occasionally found. They are usually of small size, and rarely give rise to symptoms. In a few cases they have been of the size of a man's fist, and when situated at the pylorus or ileocecal valve, caused obstruction. In other cases they have led to intussusception. In the submucosa of the respiratory tract fatty tumors are more rare. Fatty polypi are sometimes seen in the laryngeal and nasal mucosa.

Intermuscular.—Fatty tumors are occasionally found between the muscles, arising in the intermuscular connective tissue. They may reach a very large size. The myxolipoma is the most common form, and is characterized by a tendency to become sarcomatous. They are found most frequently in the gluteal folds, thigh muscles, and muscles of the neck. Congenital lipomata have been found in the muscles of the anterior abdominal wall. Enlargement of the sucking disc may give rise to a lipomatous tumor.

Periosteum.—Lipomata of the periosteum are rather rare. As a rule, they also contain striped muscle fibres, and are therefore to be regarded as heterotopous teratomata. In some cases parosteal lipomata have been observed at birth.

Joints.—A diffuse subserous hyperplasia of fatty tissue is not uncommon in the synovial membranes of the joints, the knee- and shoulder-joints being most frequently affected. The hyperplasia of the villous fringes gives

rise to an arborescent appearance (*lipoma arborescens*). The movements of the joints may be affected. These conditions are not to be classed with the true lipomata.

Internal Organs.—Lipomata are found more frequently in the kidneys than in any other of the internal organs. The tumors may arise either from the fatty or fibrous capsule, or from the interstitial connective tissue of the

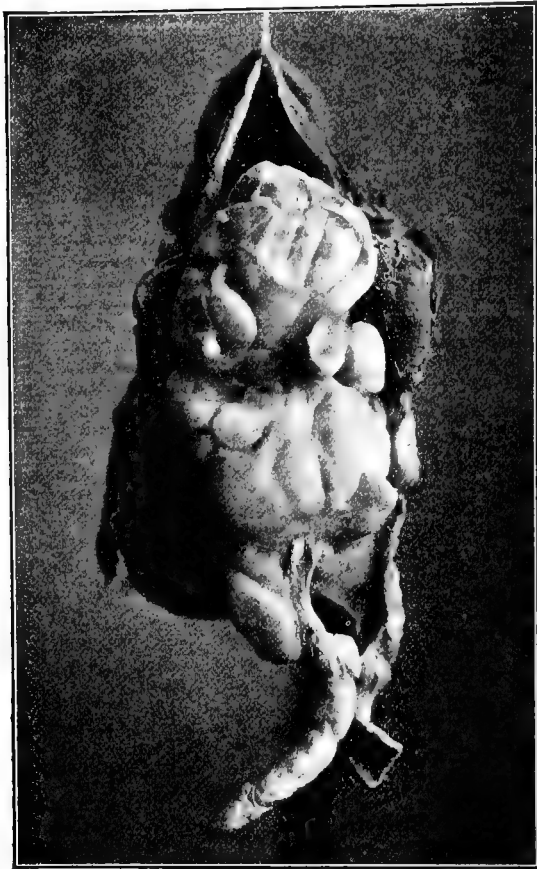


FIG. 5188.—Fibrolipoma of the Kidney. (Warthin.)

cortex and medullary pyramids. They are usually of small size, but occasionally become so large as to be of clinical importance. In the capsule the tumors may represent local fatty hyperplasias or metaplasias; in the kidney cortex they are probably heterotopous teratomata, though it is possible that they arise in some cases directly from the interstitial connective tissue of the organ or represent a metaplasia of a fibroma or of a mass of scar tissue. Many growths described as kidney lipomata were in reality "adrenal rests." The writer has reported a unique case of fibrolipoma of this organ which was so large as to cause serious clinical symptoms and to require operative interference. The growth, of which an illustration is here given (Fig. 5188), was a lobulated mass fourteen inches long, eight inches wide, and six inches in thickness, weighing two pounds. It completely filled the enormously dilated pelvis of the left kidney, and sent a round cord-like prolongation down into the dilated ureter. The only remains of kidney tissue were found microscopically in the cyst wall enclosing the tumor, which was entirely free except for a pedicled attachment posteriorly. At this point the tissues of the tumor passed into those of the cyst wall. Microscopically the tumor presented the structure of an oedematous fibrolipoma, its surface being covered with a layer of atrophic transitional epithelium derived from the kidney pelvis.

Lipomata of the heart are very rare. The majority of cases reported as such were most probably conditions of excessive fatty infiltration. According to Orth, small lipomata are sometimes found under the epicardium near the apex. Albers, Banti, Handford, Pasini, and others have reported the occurrence of lipomata arising in the intermuscular connective tissue. The cases described as lipomata of the liver and spleen are very doubtful. Those found upon the capsule of these organs probably represent portions of omentum or epiploic appendages that have become loosened. A formation of adipose tissue may occur also in old adhesions. Lipomata of the ovary have apparently not yet been observed. In the uterus tumors of the nature of lipomyoma or fibrolipoma have been seen in a few cases. Fatty tumors of the broad ligament are very rare. Very large lipomata are occasionally seen in the vulva. They may increase in size during pregnancy. Small ones are found rarely beneath the skin of the scrotum. Connected with the spermatic cord there are found sometimes lipomata of considerable size. Some of the smaller tumors of the cord described as lipomata may have been adrenal tissue (adrenals of Marchand). In the central nervous system lipomata are found rarely. They arise usually from the meninges, but fatty tumors have been found in the substance of both brain and cord. In the case of the brain, they appear to be found most commonly in connection with the corpus callosum. They are probably of the nature of heterotopous teratomata. In the complex teratomata of the nervous system a large part of the tumor mass may be made up of fat tissue. Fatty tumors are also not infrequently found in the sacral and lumbar regions in connection with spina bifida occulta.

Retrograde Changes.—According to Virchow, it is not rare to find in lipomata isolated cavities the contents of which are partly fluid and partly saponified. Saponifying necrosis of lipomata has been reported by a number of observers ("soap cysts," "butter cysts"). The necrotic areas appear whitish, opaque, and of a cheesy consistence. Lime salts may be deposited in such necrotic areas, and in this way there may be formed calcareous nodules throughout the growth. A deposit of lime salts may occur also within the stroma of the tumor. In some cases the entire growth may become calcified. Ossification has also been reported as occurring within lipomata. Liquefaction of portions of the fat tissue may occur. Through the rupture and confluence of fat cells pseudocysts filled with oil may be formed (oil cysts). The twisting of the pedicle of a polypoid lipoma may lead to the necrosis and sloughing of the entire tumor. Self-healing may result in this way. In some cases a serous atrophy of the fat tissue takes place, the tumor assuming the character of an oedema and partial liquefaction of the fat tissue. The fat may be removed from the cells and the lipoma changed into a fibroma. Myxomatous degeneration converts the tumor into a myxolipoma. This is the most common retrograde change occurring in fatty tumors; and is of the nature of a metaplasia. Retrograde changes are most common in the lipomata of the skin, since in this location the tumors are most exposed to injury and to the possibility of infection.

DIAGNOSIS.—The nature of the gross appearances, the clinical history, etc., make the diagnosis easy in those cases in which the tumor can be seen and directly palpated. The subcutaneous lipomata are slowly growing, lobulated, movable tumors, and give pseudofluctuation. In the case of large lipomata of the internal organs the negative results of aspiration in the case of a fluctuating tumor would lead to the suspicion of lipoma, particularly in the case of retroperitoneal tumors. The presence of inflammatory changes and the development of cachexia are suggestive of sarcomatous change. Neuralgic pains may be associated with lipomata. The symptoms in general are dependent upon the position and size. Lipomata of internal organs may give rise to important pressure symptoms. In the great majority of cases, however, the only effect is a cosmetic one. In spite of the

great size to which they frequently attain lipomata do not usually influence the general metabolism of the body.

PROGNOSIS.—The prognosis in lipoma is favorable. Since this form of tumor produces no metastases it must be classed with the benign neoplasms. Sarcoma may develop in a lipoma, but this occurrence is very rare, more so than in the case of any other of the benign connective-tissue tumors. Sarcomatous change appears to be more common in the case of tumors containing both adipose and myxomatous tissue (myxolipoma), the resulting sarcoma being of the nature of a myxosarcoma. This change occurs most frequently in lipomata of the intermuscular connective tissue. The cases reported in the literature as metastatic lipomata are undoubtedly examples of sarcomata containing fat tissue. No evidence exists of the metastasis of a pure lipoma. As a rule, the growth of a lipoma is gradual and slow, with periods of apparent quiescence. In the case of infected lipomata, particularly those of the skin, the prognosis is more grave, since the conditions favor the occurrence of phlegmonous inflammations with resulting septicæmia or pyæmia. Such complications are, however, on the whole rare. In the case of large lipomata of internal organs the prognosis depends upon the location of the growth, the extent of the pressure symptoms, the organs thus involved, etc. The removal of a lipoma usually results in a cure, recurrence being very rare.

TREATMENT.—The treatment is purely surgical. In the case of subcutaneous lipomata local anæsthesia is usually sufficient. It should be borne in mind that the capsule should be removed in all cases of lipoma, since very often the new formation of fat tissue proceeds from the fibrous capsule. In the case of the diffuse forms the prolongations of fatty and fibrous tissue extending into the surrounding tissues should be dissected out, as from these a recurrence may take place. In those cases in which the tumors are covered by atrophic or inflamed skin the incision is best made at the base of the growth and not over it. Tearing should be carefully avoided. Drainage is not necessary. The strictest aseptic precautions should be observed during the operation and afterward, since the condition of the tissues about the growth favors infection and the occurrence of phlegmonous inflammations.

Alfred Scott Warthin.

LIVER, TUBERCULOSIS OF THE.—Without exception all writers agree as to the rarity of primary tuberculosis of the liver, a number going so far as to affirm that an undoubted case of primary hepatic tuberculosis has not yet been reported. Such an apparent immunity on the part of this organ to tuberculous infection cannot be explained by any lessened opportunities for infection, as compared to other organs, such as the kidneys, testicles, etc., in which a primary tuberculosis of clinical importance is not so rare. Indeed, it would appear that the liver with its large extent of vascular surface and the relatively slow circulation in its blood spaces would stand a very good chance of infection from tubercle bacilli that have gained a cryptogenic entrance into the blood stream. Further, the fact that tubercle bacilli may be taken into the alimentary canal in the food and drink would lead to the supposition that the portal veins would constitute one of the avenues of tuberculous infection. These considerations would make it seem probable that primary hepatic tuberculosis would occur more often than we actually find to be the case. It is the opinion of the writer that small healed primary tubercles not infrequently occur in the liver. As is well known to every pathologist, small nodules of hyaline connective tissue varying in size from that of a pinhead to that of a pea are not rare in this organ. By the majority of writers they have been regarded as small fibromata or healed gummata. The fact that some of these little nodules consist of a caseous centre surrounded by a connective-tissue capsule, and that others present an earlier stage of caseating epithelioid tissue with beginning encapsulation, has led the writer to regard the majority of such nodules as healed tubercles. Similar small fibroid nodules are also

frequently seen in the spleen and kidneys and are similarly interpreted. If the probabilities of infection, the not infrequent occurrence of healed tubercles, and the extreme rarity of primary hepatic tuberculosis of clinical importance be considered, it would seem that the liver possessed a relatively high resistance to tuberculosis.

Such a relative immunity undoubtedly exists in the fetal liver. A number of cases have been reported of maternal tuberculosis in which the liver of the fœtus contained great numbers of tubercle bacilli (as shown by staining and animal inoculation) without histological lesions of tuberculosis. Such a case has recently been reported by the writer. The seven-months fœtus of a woman dying from acute miliary tuberculosis was examined carefully for evidences of congenital tuberculosis. The placenta presented a marked miliary tuberculosis. Tubercle bacilli were found in the hepatic vessels of the fœtus, and the inoculation of a guinea-pig with an emulsion of fetal liver gave positive results. Agglutination thrombi were found in the liver capillaries, but no histological evidences of tuberculosis. Several cases, however, have been reported of probable congenital tuberculosis in which tuberculous lesions were found in the liver, the infection being regarded as taking place through the umbilical vein from the placenta. These cases are therefore to be classed as primary hepatic tuberculosis.

If primary tuberculosis of the liver is rare, secondary involvement of this organ is one of the most common pathological findings. Not only in cases of acute miliary tuberculosis are great numbers of tubercles found in this organ, but also in all advanced cases of chronic pulmonary and bone tuberculosis. Even in cases in which the disease of the lung is not very extensive scattered secondary tubercles may be found throughout the liver. As a rule, these secondary tubercles are very small, and as it is rarely possible to recognize them by the naked eye at autopsy, they are frequently overlooked. In the great majority of cases their presence can be demonstrated only by microscopical examination. The larger ones (size of a mustard seed to that of a pea) are grayish, semitranslucent, with yellowish opaque centres. They can be best seen in the livers of children where they often are several millimetres in diameter. The infection is usually hæmatogenous, and the microscopical picture presented is that of a disseminated miliary tuberculosis of the organ. Occasionally larger caseous nodules are found in connection with miliary tubercles, and more rarely tuberculous cavities or abscesses. Still more rarely there are found large solid caseous nodules in the liver resembling the solitary tubercles of the brain. These may be mistaken for cancer nodules or gummata. Such large nodules may not show any especial connection with the bile ducts, and it is probable that in some cases they represent primary tubercles.

The number of the miliary tubercles may be so great that each section may be full of them; in other cases it may be necessary to examine many sections before a tubercle is found. In the case of pulmonary and bone tuberculosis and general miliary tuberculosis the infection of the liver is usually through the hepatic artery; in the case of intestinal tuberculosis it may take place through the portal vein or lymphatics. The tubercles, in infection either through the hepatic artery or through the portal vein, are found chiefly at the periphery of the lobule and in the interlobular connective tissue. A small number may be found in the intermediate and central zones of the lobule. As the nodules increase in size they extend in from the periphery and cause a destruction of the liver cells.

The writer believes that in the great majority of cases the earliest step in the formation of a liver tubercle is an agglutination thrombosis in the liver capillary. The deposit and growth of tubercle bacilli upon the endothelium of the capillary wall and the consequent injury to the endothelial cells are probably chiefly responsible for this thrombosis. As a result of the thrombosis and of the injury to the endothelium, as well as from the formation of toxins, the neighboring liver cells undergo

degeneration or necrosis. There is a collection of leucocytes at the affected point, and these may also undergo necrosis. Following the degenerative changes there is a proliferation of the endothelium and of the neighboring connective tissue leading to the formation of an epithelioid tubercle which sooner or later shows a central caseation. The smallest tubercles may show no inflammatory reaction about them. Giant cells may be present in large or small numbers, or may be entirely absent. They arise from the proliferating endothelial and connective-tissue cells, and possibly also from the leucocytes. As the nodules increase in size they may become confluent. As the result of an interstitial infiltration about the tubercles the picture of a diffuse cirrhosis may be presented, newly formed connective tissue being found not only between the lobules, but also growing into the latter. The greater the number of tubercles the closer the resemblance to a cirrhosis. An increase of the small bile ducts may be observed in the neighborhood of the tubercles. A true atrophic cirrhosis may result, but usually death occurs before this condition has time to develop. It should be remembered also that the tuberculosis may occur secondarily in a cirrhotic liver.

In very acute cases of general miliary tuberculosis with a high degree of virulence the only lesions found in the liver may be areas of focal necrosis of the liver cells. These areas may be so large as to be easily seen with the naked eye. The blood spaces of the necrotic areas are filled with fibrin and agglutinated red cells. Large colonies of tubercle bacilli may be found in the necrotic foci. No proliferation of the endothelium or connective tissue may be present; giant cells are entirely absent. The process can be recognized as tuberculosis only by staining for tubercle bacilli. The writer has seen two cases of this kind which were diagnosed as typhoid fever; the autopsy showed large focal necroses in liver, spleen, and kidneys, those in the liver and spleen being most numerous and largest. No epithelioid proliferation or giant cells were found about these areas, and the tuberculous nature of the process was recognized only on staining for tubercle bacilli, when each caseous focus was found to contain great numbers of the latter. In general miliary tuberculosis of a less virulent type small focal necroses of this kind are also found in association with epithelioid, lymphoid, and caseating tubercles. It is also to be noted that in such cases the lesions in the liver are usually smaller than in other organs, and this fact may also be taken as an indication of a greater resisting power on the part of the liver to tuberculosis.

In the case of hepatic tubercles occurring secondarily to chronic tuberculosis of other organs the liver may show such changes as amyloid and fatty infiltration. The latter change is practically always present. In chronic pulmonary tuberculosis the liver shows usually a more or less marked chronic passive congestion (nutmeg liver). In acute miliary infections the liver cells show cloudy swelling, fatty degeneration, or simple necrosis.

Hanot and Gilbert distinguish the following forms of hepatic tuberculosis:

1. Acute hépatite tuberculeuse graisseuse hypertrophique.
2. Subacute. (a) Hépatite tuberculeuse graisseuse atrophique ou sans hypertrophie; (b) hépatite tuberculeuse parenchymateuse nodulaire.
3. Chronic. (a) Cirrhose tuberculeuse; (b) foie gras tuberculeux (without tubercles).

A rare complication of hepatic tuberculosis is secondary carcinoma of this organ. Several cases of this kind have been reported, and the writer has seen a similar case in which both the tuberculous infection and the metastasis of the carcinoma were through the portal vein.

More rare than secondary miliary tubercles of the liver are larger caseous nodules, the centres of which contain cavities filled with bile-stained caseous material. These cavities may be of the size of a walnut. The process represents a tuberculosis of the bile ducts, the walls of which become caseous. The infection is probably

lymphogenous, and has the character of a tuberculous periangiocholitis. In very rare cases the infection may take place through the bile ducts themselves. In the great majority of these cases, however, the tuberculous process begins around the bile duct and invades its mucosa only secondarily. Hæmatogenous hepatic tubercles may or may not be associated with this condition.

The liver and the peritoneum may be involved at the same time, but this organ is rarely involved from the latter or from the omentum.

In experimental hepatic tuberculosis in animals the process runs a more acute course, being characterized by larger areas of necrosis.

The clinical symptoms of hepatic tuberculosis are slight, and the condition can but rarely be distinguished from the miliary or chronic process with which it is associated. The occurrence of icterus or the rapid development of a painless ascites points to the development of tuberculosis of this organ. In children the organ may become enlarged and sensitive. *Aldred Scott Warthin.*

LOÈCHE-LES-BAINS (LEUKERBAD).—Loèche-les-Bains is situated in Switzerland at the foot of the Gemmi Pass, at an altitude of 4,600 feet. The nearest railway station is distant three and a half hours' drive. The little village of Leukerbad is picturesquely situated in a narrow valley about a mile and a half wide and twelve miles long, open to the south and surrounded on the northwest and east by lofty snow mountains, and hills on whose spurs flourish the pine and fir. Through the valley runs the glacial stream, the "Dala," on one bank of which is situated the village and on the other the baths. The climate is a mountain climate, changeable as to weather and temperature, with cool mornings and evenings. Sometimes snow falls in June and August. Patients should, therefore, be provided with warm clothing. The mean temperature for June, July, and August is about 30° F., the mean minimum 6.8° F., and the maximum 45.7° F.

There are various mountain excursions in the vicinity of greater or less extent, and from here a bridle path leads over the Gemmi Pass to Kandersteg, affording impressive views of Alpine scenery. The season lasts from June 18th to September 30th.

The waters of Loèche are classed as simple thermal waters, the natural temperature being from 102° F. to 104° F. They contain, however, 1.9 solids per litre, of which 1.4 is calcium sulphate, and hence could be classed with the *earthy* group.

They are employed for both drinking and bathing, chiefly the latter. Both the short and the prolonged baths are used, particularly the latter, which are a specialty of Loèche. They are taken at a temperature of 93° F. to 95° F., and last from one to six hours. For the most part piscines or large tanks are employed where members of both sexes, clothed in woollen garments, bathe, a partition separating the sexes. Games, such as chess, dominoes, checkers, etc., are played on small floating tables, and the same are used for serving light refreshments.

Patients are advised to wait a few days before beginning the baths in order to become acclimatized and recover from the fatigue of the journey. After taking these baths for ten or eleven days, a sort of dermatitis appears on the skin, varying in intensity and accompanied sometimes with a rise of temperature and anorexia. This eruption usually persists from ten to fourteen days; it is called the "poussée."

The prolonged baths are beneficial in chronic skin affections, such as eczema, psoriasis, chronic urticaria, lichen, acne, etc. They are also employed in cases of chronic rheumatism and gout in combination with douche massage. Affections of the pelvic viscera, chronic catarrhal conditions of the mucous membranes of the digestive, respiratory, and sexual organs, anæmia, and some nervous disorders are also said to be benefited by these waters, and in these cases the short baths are indicated.

July and August are the chief months for the cure, and during this period the patients arrive at the baths at five o'clock in the morning and generally take a cup of tea or coffee in the bath. After the bath they go to bed for half an hour, subsequently take a short walk, and at eleven o'clock take a regular meal. At about three p.m. the bath and rest in bed are repeated, and at six the principal meal of the day is taken. The duration of the day's bathing is but an hour at first, which is gradually increased.

In the internal use of the waters from one to five glasses are drunk daily; the effect is diuretic and sometimes sedative to gastric irritability.

The baths are all near the hotels, with which they are generally connected by covered corridors. There are arrangements for the different varieties of douche, inhalation, pulverization, massage, etc.

The contraindications are the same in general as with other thermal baths.

The accommodations are good and reasonable.

Edward O. Otis.

MARASMUS.—(Synonyms: Infantile atrophy, Athrepsia, Simple wasting; German, Darmatrophie.)

DEFINITION.—Marasmus may be described as progressive wasting in infants without discoverable organic cause.

SYMPTOMS.—The striking feature of the condition is failure to gain in weight or slow but progressive loss in weight. Meanwhile increase in length of the bony skeleton and the eruption of the teeth proceed at almost the normal rate; so that the resulting appearance is peculiar and characteristic. The body is thin and

few minutes after the taking of food. The stools may be large or small; in recent cases they may show evidences of indigestion, but in well-developed cases that are properly managed the stools are smooth and contain neither curds nor mucus. Their color depends upon the food being administered. Cases in which there is diarrhoea are complicated by intestinal indigestion or inflammation. The fontanelle is depressed to a greater or lesser degree, the temples are sunken, the mouth and tongue are dry and in advanced cases glazed and covered by patches of thrush. The intercostal spaces are depressed so that it is impossible to use a stethoscope satisfactorily upon the front and sides of the chest. The skin becomes thin, loses its elasticity, and hangs in folds particularly on the abdomen and on the inner sides of the thighs. The abdomen may be either distended in cases where indigestion is present, or it may be flaccid and depressed as is usually the case with patients who are being carefully fed. There is enlargement of the liver discovered by palpation, but no enlargement of the spleen. Movements of the intestines, particularly the colon, are readily observed through the abdominal wall. The temperature is apt to be subnormal, 96° to 97° F. in the rectum being a common reading. The extremities are cold. The superficial lymph nodes on the abdomen, in the groins, in the axilla, and in the neck are frequently somewhat enlarged.

On account of the extreme emaciation, there is a great tendency to the formation of bed-sores upon the sacrum, the crests of the ilium, and the back of the head, so that constant change of position is absolutely necessary, together with the greatest care of the skin in these situations. Petechiae may develop, usually



FIG. 5180.—Marasmus. Infant seven months old. Weight seven pounds—half a pound less than the birth-weight.

markedly emaciated, all the subcutaneous fat having disappeared except the sucking pads in the cheeks; so that the bones and muscles are plainly made out through the loosely hanging skin and the face takes on the appearance of an old man. The color is pale or yellowish gray; the eyes have an anxious expression, and the child is looking about in search for food and is putting its fingers into its mouth or grasping at anything near by to suck. There is a constant fretful cry which later becomes a whine. Very young infants may not even cry, but sleep most of the time, so that the family is lulled into a false sense of security. These infants are always hungry, and the hunger is not appeased for more than a

first upon the abdomen; they are not necessarily of bad prognostic significance, for I have seen recovery in even the severest cases.

There is a peculiar tendency of these infants to develop suddenly a general oedema. This appears first in the feet, hands, and eyelids, and then extends to the genitals and the rest of the body. Frequently the first sign of such developing oedema is a sudden gain in weight of three or four ounces in twenty-four hours; so that one is always suspicious that any gain of several ounces in twenty-four hours will prove to be spurious and due to this condition.

The weight of marantic infants is of course far below

the normal for their age. We frequently see infants suffering from this condition whose weight at six months or later is less than their birth weight. I have frequently had babies at six months weighing six pounds and not uncommonly those at one year with a weight of ten pounds. On account of the growth of the skeleton in length, these infants appear to weigh less than they actually do.

Physical examination of the chest sometimes reveals a slight blowing cardiac murmur; at other times a loud congenital heart murmur is found. At the back of the chest between the scapulae there are frequently heard, especially in advanced cases, fine crackling râles, which are due to hypostatic congestion, the result of the feeble circulation and of lying upon the back.

The emaciation continues until assimilation is re-established; but the baby will remain fretful and even hungry until the weight increases to within a couple of pounds of what is normal for the infant's age.

If no improvement takes place the baby dies either from exhaustion or from some intercurrent disease, particularly acute gastroenteric infection, broncho-pneumonia, or sepsis from infection arising at the sites of decubitus ulcers.

In many cases there is a peculiar tendency to hold the head retracted in a condition of cervical opisthotonos, and there is also a tendency of the extremities to be held rigid in a condition of semiflexion, resulting in the presence of Kernig's sign and leading falsely to the diagnosis of tuberculous meningitis. This rigidity diminishes and disappears as the nutrition of the child improves and as the fontanelle resumes its normal level.

DIAGNOSIS.—The condition must be distinguished from congenital syphilis, pyloric stenosis, tuberculosis, and acute inanition.

PATHOLOGY.—Very careful studies have been made of hundreds of cases of marasmus, but the findings do not satisfactorily explain the condition. The question always arises whether the post-mortem conditions are the cause or the result of the prolonged wasting. The constant lesions found in the alimentary tract are a marked thinning of the intestinal mucous membrane with atrophy of the intestinal villi and tubules. The stomach is often dilated and its mucous membrane coated with tenacious mucus. In some cases there has been found hyperplasia of the epithelium and connective-tissue infiltrations of the mucous membrane of the intestines together with atrophy of the glandular substance. The solitary and agminated follicles are frequently somewhat swollen and pigmented, presenting the so-called "shaven-beard" appearance, and there may be some enlargement of the mesenteric-lymph nodes. Bloch (*Jahrbuch f. Kinderheilkunde*, 1904, lix.) found that Paneth's cells in the ducts of Lieberkühn contain few or none of the granules which are regarded as indicating that the cells have normal functional power. The liver is often found much enlarged and fatty. The lesion under the microscope is shown to be a fatty infiltration. According to Holt, this lesion is not more frequent in marasmus than in infants dying from other diseases, so that too much must not be made of this finding. The brain is anæmic. Thrombi are rare. The heart muscle is pale and thin; the kidneys may show parenchymatous degeneration, but are commonly normal. Hypostatic congestion of the lungs along the posterior strips is common.

PATHOGENESIS.—The essence of the condition seems to be a failure of absorption or assimilation or both combined. In numerous instances there is added an auto-intoxication by decomposition products absorbed from the intestine. The existence, however, of cases in which there is no discoverable evidence of indigestion, and in which a quantity of food sufficient or more than sufficient for the caloric needs of the infant is being taken and digested, proves that some interference with absorption and assimilation is present. Absorption depends, of course, upon the epithelium in the intestinal wall, and perhaps upon the intestinal juices, while assimilation

depends upon chemical processes, most likely ferment action in the body cells. The atrophic condition of the intestinal wall, together with the fatty condition of the liver, has been thought by many to explain this failure of absorption and assimilation. It is not certain, however, that the atrophy of the intestinal wall may not be a result of the starvation rather than its cause.

Another theory is that the condition is the result of infection, and that it can be communicated from one child to another. In support of this are brought forth the cases in which marasmus develops in several infants in a hospital ward. Against this theory it is to be remarked, however, that such infants are prone to develop marasmus because of "hospitalism," and that the condition also develops in private practice where there are no other children to give the infection. Keller thinks the condition is frequently an acid auto-intoxication; undoubtedly this is true in some cases. Wentworth ascribes the condition to lack of the only food, i.e., breast milk, capable of adequately activating the digestive functions.

Perhaps the best explanation of the condition is that recently proposed by Edsall (*Journal of the American Medical Association*, May 4th, 1907). His idea is that the defect is one in the ferment action of the intestinal wall and of the body cells. In the process of metabolism food-stuffs are broken down into simpler products by ferment action, are absorbed, changed into the forms in which they circulate in the blood, and built up into human tissue also by ferment action. The catabolism and the anabolism are carried on, in many instances, by the same ferment, the action in the two cases being merely reversed. It is probable, according to Edsall, that, except with human milk as the food, the ferment action of catabolism is incomplete, and that the end products of proteid digestion are not suitable for being built up into human proteid. The infant can use the heterologous proteid for obtaining energy, but cannot use it for building up its own body cells, since this requires homologous proteid. Moreover, since the ferment that causes the final breaking down of foreign proteid and the initial building up of the fragments into homologous proteid is the same (the action in the latter instance being merely reversed), and since, moreover, this catabolic ferment is deficient in its power, necessarily the anabolism is likewise defective, and the baby fails to grow.

ETIOLOGY.—In considering the etiology it must first be noted that this condition occurs almost wholly in the first year of life and in the majority of the cases during the first six months. It is very rare among breast-fed infants and is commonest in artificially fed babies that have had an attack of gastroenteritis, particularly those that live in institutions or homes for infants. It is therefore met with most frequently during August and September. The condition does occur in private practice, but is rather rare.

Etiologically the cases can be divided into (a) those that are secondary to congenital syphilis, congenital heart disease, tuberculosis, and acute pulmonary inflammations; (b) those in which the malnutrition is a symptom and result of the existing gastroenteric inflammation or indigestion; and (c) those that give no evidence of any organic or functional abnormality save the failure of assimilation. It is only the last class of cases that this article considers. These cases in turn may be divided into those due to congenital debility or insufficiency of the assimilative function, such that not even breast milk, let alone cow's milk or other food, can be utilized; and those that arise after a period of gastroenteric indigestion or inflammation, generally the result of withdrawing breast milk or of inability to adapt the modified cow's milk to the digestive capacity of the baby. It is to be kept constantly in mind, however, that after this condition of marasmus is once established the infant may show absolutely no signs of any digestive disturbance, and the function of the stomach and bowels may be performed with apparent perfection, there being

no vomiting or colic, no excess of gas, and the stools appearing perfectly normal. Moreover, in many cases the absorption of the food seems satisfactory, the stools not being more copious than in normal infants taking the same quantity of food.

Some change in the food, particularly the substitution of breast milk, either wholly or in part, for the previous diet may tip the scale for the better with the result that the infant begins to gain in weight and progress, and the recovery is steady although sometimes slow. These cases where recovery occurs upon the addition of breast milk to the diet would support the theory of Edsall or that of Wentworth that the pathogenesis of the condition lies in the insufficiency of ferment action or inability to activate the digestion. Another class of cases will improve upon the addition of pancreatic ferments to the food, or upon the addition of malt diastase. These also would bear out these theories. Still another class of cases will not improve until alkalies are added. These cases bear out the contention of Keller, who considers the condition largely an acid autointoxication.

TREATMENT.—Feeding. The consideration of the etiology of the condition as well as the results of practical experience make it evident that *prophylaxis* is best obtained by promoting so far as possible the breast-feeding of all infants, particularly those that are congenitally weak, and those that have suffered from severe gastrointestinal or other disorders. Next best is the careful adaptation of modified cow's milk to the digestive capacity of the infant, with particular caution against the use of all mixtures rich in fat, which so often result in acid autointoxication, and with caution also against overfeeding.

When the condition is once established, breast-feeding should be advised in all cases, and the breast milk should be adapted to the digestion of the infant either by the use of simple diluents (such as water, barley water, or either with lime water added) given before the nursings, or by the use of some of the digestive ferments suspended in lime water or barley water. Combinations of the ferments seem to give the best results. In the great majority of cases, breast-feeding will result in a speedy improvement of the baby. It is often necessary, in order to secure the best results, that the wet-nurse's baby should continue to nurse its mother so that the breasts may have a sufficiently strong nursing stimulus to keep up the activity of the glands. If it is impossible to get a wet-nurse, it is at times possible, nevertheless, to obtain breast milk for some of the feedings, or to have the baby nursed once or twice each day. On account of the ferments in the breast milk and on account of the ease with which the breast-milk proteids can be digested and built up into human tissue, even a little breast milk is of great value. According to Wentworth, the breast milk increases the amount of hydrochloric acid and of secretin, and these in turn activate the pancreas.

When it is impossible to obtain any breast milk, one must continue with artificial feeding. According to the most improved methods of milk modification, the milk should be fresh, clean, and raw. Inasmuch as these babies do not digest fat satisfactorily, a mixture having a low percentage of fat should be used. Top-milk mixtures and mixtures of cream and milk are therefore not so satisfactory as mixtures made from whole milk or even from skimmed milk. The resulting formula should have the percentage of fat not higher than that of the proteid. For instance, a healthy baby of three months would probably be taking six or seven feedings daily of $3\frac{1}{2}$ to 4 oz. of modified milk, whose composition would average 3 per cent. fat, 6 to 7 per cent. sugar, and 1.5 per cent. proteid. The marantic baby of the same age weighing seven or eight pounds would probably do better upon eight feedings of 3 to $3\frac{1}{2}$ oz. each, of a formula: 0.5 to 1 per cent. fat, 6 per cent. sugar, and 1 to 1.5 per cent. proteid. It is often advisable to peptonize this food, and if the baby is over three months old to use barley water as a diluent instead of

plain water. Frequently it is wise to use whey and milk in making the mixtures in order to increase the quantity of soluble proteid therein; for instance, in making up a quart of modified milk, instead of using 8 ounces of mixed milk, it would be wiser to use 4 ounces of mixed milk and 12 ounces of whey, together with the required amount of milk sugar and water or barley water. In this way the percentage of the easily digested lactalbumin is increased. At times it may be necessary, for a short period, to use whey alone or even peptonized whey. The whey should not be continued for a long time, however, because it lacks the nucleoproteid contained in the casein of the milk. If the baby is not satisfied with the food, first the quantity and then the strength of the food may be increased, care being taken to make any change gradually. The whey can gradually be replaced by milk, and in cool weather, for the sake of its higher caloric value, by top milk of increasing fat percentage. This can be substituted an ounce at a time for the mixed milk or for the skimmed milk.

If the peptonized modified milk does not result in a relief of symptoms and gain in weight, it is of advantage in cases where there is neither vomiting nor diarrhoea to make use of Keller's malt-soup mixture. This is a modification of cow's milk made up with wheat-flour gruel and a specially prepared alkaline malt extract. Keller's directions are to take 3 ounces of specially prepared malt extract containing potassium carbonate (made by Loefflund and known as Loefflund's malt-soup extract) and to dissolve this in one pint of water. Two ounces of wheat flour are suspended in a pint of milk, thoroughly stirred and drained through cheese cloth. The malt-extract solution and the milk containing the flour are then mixed in a vessel and set over the fire for about one-half hour, being stirred constantly. When the mixture begins to boil, the food is removed and put into the feeding bottles. The mixture contains dextrinized cereal and maltose in addition to the milk which has been sterilized.

The writer has had personal experience with this form of feeding in his hospital and private cases for over two years, and has found it oftentimes of the greatest value. Usually, however, at the outset the milk and flour should be employed in about one-half the quantities mentioned, otherwise some indigestion, shown either by loose stools or by vomiting, may result. As the infant becomes accustomed to the new food, the quantity of the flour and of the milk can be safely increased.

General Hygiene.—These infants require intelligent care; they must be kept warm, but must not be crowded in close rooms. Plenty of fresh air, day and night, is absolutely essential, so that the infants must be kept out of doors or on a balcony as much as possible. The skin must be kept clean by a daily bath, after which an inunction of equal parts of olive oil, cod-liver oil, and lanolin should be made. In winter it is often necessary to wrap the extremities in cotton, as one would swathe a premature infant; hot-water bottles should be kept at the feet and mittens on the hands to prevent the extremities becoming chilled.

Special Treatment.—As an aid to the dietetic treatment it is sometimes advantageous to administer minim doses of dilute hydrochloric acid after the feedings. If stimulation is needed heat to the extremities, nuxvomica by mouth, and hot saline irrigations of the colon are most efficacious. The colon irrigations may be given every day or two, as they seem to retard the loss in weight. If oedema develops, all salt should be withdrawn from the food and saline irrigations discontinued. An increase in the proteid content of the food should be made and any irrigations used should be of plain warm water. The oedema seems to depend in some cases upon salt being retained in the tissues, in others upon lack of proteid in the food.

Frequent change of position and attention to the diapers are necessary to prevent the development of bed-sores, as well as to prevent hypostatic pneumonia. If bed-sores develop they must be treated on surgical

principles. Thrush is best combated by painting the mouth every second day with one-per-cent. formaldehyde solution, and by using a solution of bicarbonate of sodium or of borax subsequently as a mouth wash.

Careful study of the digestive peculiarities of the infant, together with the careful application of our present knowledge of the pathogenesis of this condition, will result in the saving of many cases formerly considered hopeless.

Linnæus E. La Fétra.

MESOTAN is the methyloxymethylester of salicylic acid, $C_6H_4(OH)COOCH_2OCH_3$. It is a yellow, aromatic oily fluid, of a specific gravity of 1.2 at 15° C. Slightly soluble in water, fairly so in alcohol, ether, chloroform, and fixed oils. It decomposes at 100° C. with the liberation of salicylic acid, formaldehyde, and methyl alcohol. It is somewhat unstable when exposed to the air and should therefore be kept in well-stoppered bottles.

Mesotan is absorbed through the skin, liberating salicylic acid, and thus acts directly upon the affected part, relieving pain and swelling. When applied to the skin it is apt to cause an irritation preceded by a burning sensation. It is best diluted with fifty per cent. of olive oil, and is used as an external application in muscular and articular rheumatism, acute or chronic, as well as in gout and neuralgia. It should be applied without friction in fifty-per-cent. mixture, two or three times a day. The part should be lightly covered.

John W. Wainwright.

MICTURITION, DISORDERS OF.—Given normal urine and a normal genito-urinary tract, micturition is accompanied and followed by no other sensation than one of relief, and is performed normally from four to twelve times in twenty-four hours, depending upon the temperature and humidity of the air, the amount of exercise taken, the intensity of the mental occupation and the degree of anxiety which it entails, the volume of water drunk, and upon the kind of food ingested.

For convenience in reference, the disorders of micturition are given alphabetically; but the several possible causes of each disorder are arranged as nearly as possible according to the frequency of their occurrence.

Diminished Stream.—This disorder may be either (1) temporary, or (2) constant until relieved by surgical intervention.

1. When temporary or of short duration a diminution in the size of the stream points to a transient obstruction, *e.g.*, congestion at some point or zone in the urethra or a urethral spasm.

As a result of inflammation, any part of the urethral canal may become swollen to the extent of obstructing the urinary stream to a greater or less extent. Thus we may have a diminished stream due to a severe acute urethritis affecting the anterior urethra, with or without involvement of the posterior urethra. It may also be observed in connection with an acute prostatitis.

Any lesion of the urethra—*e.g.*, organic stricture, especially if irritable, or a granular patch—is capable of exciting urethral spasm, especially in neurotic individuals. The diagnosis must be made partly by exclusion, but chiefly by exploration of the urethra with a bougie-à-boule, sound, and endoscope.

2. A diminished stream which either shows no tendency to grow larger or undergoes a progressive further diminution in size, points to an organic obstruction. In all cases of this nature of long standing the resulting atony of the bladder plays an important though secondary part in the character of the stream.

Organic stricture, when neglected, gives a stream which tends constantly but slowly to diminish in size. If the stricture be situated at or near the meatus the stream will be small and scattering, but forcible; if it be situated deeper within the canal, the forcible projection will be lacking. When the stricture becomes inflamed from any cause, the diminution progresses rapidly and may persist until complete retention results.

Prostatic enlargement has among its early symptoms a diminution of the urinary stream. As micturition begins, the stream is small and feeble, sometimes dribbling; it then becomes larger and, except in the later stages of enlargement of the prostate, attains a fair volume and force, only to become again small and feeble and usually dribbling as the act is completed.

Chronic contraction of the prostatic fibres surrounding the neck of the bladder gives the same symptoms as does commencing enlargement of the prostate. In the differential diagnosis the chief point is the age of the patient; in many cases the diagnosis cannot be made without an exploratory perineal section.

Periurethral abscess may cause a narrowing of the urethra and thus diminish the stream; when situated in the bulbous portion the abscess may cause acute retention.

A partial plugging of the urethra by a small calculus arrested on its way from the bladder produces a diminution of the stream that becomes more marked as inflammatory congestion advances. If the calculus is rough there will follow an oozing of blood from the meatus, unless the urethral mucous membrane happens to be deeply cicatricial at the point of arrest. Palpation along the course of the urethra—per rectum for the posterior portion—rarely fails to detect the calculus. Instrumental exploration usually is conclusive.

A partial plugging of the outlet of the bladder by a pedunculate tumor or a small movable calculus will give rise to a diminished stream accompanied by symptoms more or less pathognomonic of the lesion present. The diagnosis is materially aided by the fact that immediate relief is obtained by dorsal decubitus or by the dislodgement of the obstruction by means of a sound or searcher.

Urethral polypi diminish the stream in proportion to their size. When they are very small there may be no symptom except hemorrhage.

Dribbling.—In addition to the dribbling that characterizes the first and second forms of incontinence, and which is sufficiently described in subsequent paragraphs, still other types of dribbling may be recognized. Thus we have:

1. The involuntary, painless escape of a few drops of urine at the end of micturition.

2. The voluntary, not always painless, escape of a few drops of urine at the beginning of micturition.

3. The urine is voided in drops throughout micturition. (1) In prostatic enlargement the dribbling of a few drops of urine at the end of micturition is a common and early symptom. It is independent of the degree of vesical atony which may be present; in fact, it may exist without the presence of any vesical atony whatever.

In chronic urethritis (anterior or posterior or both) the dribbling, when present, is constant until the muscular tone of the urethra has been restored.

In stricture of the urethra of large calibre the final drops of urine are caught behind the stricture and dribble out into the clothing.

In chronic contraction of the prostatic fibres surrounding the neck of the bladder the dribbling at first is an intermittent symptom; later, it is constant.

(2) In prostatic enlargement the voluntary and not always painless escape of a few drops of urine occurs at the beginning of micturition. It is preceded by hesitancy and gradually gives way to the full stream, which in turn dies away and ends with dribbling.

(3) In filiform stricture of the urethra, if it has existed for a relatively short period of time, and consequently is associated with only slight atony of the bladder, the stream is of a dribbling character, and is produced with more or less effort.

In acute prostatitis (including prostatic abscess) and in acute seminal vesiculitis the urine is voided in drops when retention threatens, either from mechanical obstruction or as the result of reflex irritation.

Frequency and Urgency; Pain and Tenesmus.—Frequency of urination may be normal, or physiologic, within wide limits. It is abnormal, or pathologic, when

accompanied by urgency, pain or tenesmus, or when due to a tangible, pathologic condition or to that obscure pathologic state called a neurosis. Frequency rarely occurs without at least a trace of urgency; frequency and urgency are practically never without a degree of initial or terminal pain and tenesmus. Frequency due to quantity alone is not included, it being dependent, strictly speaking, upon a disorder of elimination.

In acute posterior urethritis, when this is severe, frequency and urgency are marked; a lesser grade gives only frequency; the mildest grade of all does not occasion any disorder of micturition. In every case of acute posterior urethritis a digital rectal examination should be made to ascertain whether acute prostatitis and acute seminal vesiculitis are present.

In chronic posterior urethritis there is, in most cases, a very trifling frequency which shows a tendency to increase and may become complicated by urgency, as well as occasionally by pain and tenesmus, during an exacerbation of the local congestion. In a few cases frequency is constant, and is accompanied by more or less urgency and slight initial and terminal pain, with very moderate tenesmus.

In organic urethral stricture the frequency is due to the maintenance of a chronic posterior urethritis. Usually it is diurnal only. Later on, chronic partial retention is added, and, the symptoms becoming exaggerated by the congestion due to this retention, urgency and possibly pain and tenesmus develop.

In acute prostatitis and acute seminal vesiculitis (including prostatic abscess) there may be, in the early stage, simply increased frequency, but usually both this symptom and urgency coexist from the outset, and with them are associated more or less pain and tenesmus. Very rarely there is no disorder of micturition. Digital rectal examination affords the only means of establishing the diagnosis.

In chronic prostatitis and chronic seminal vesiculitis a slight, uncomplicated, diurnal increase in frequency is a characteristic of the disease. It tends to increase and urgency develops during the occasional mild exacerbations to which the coincident posterior urethritis is liable.

In prostatic enlargement, uncomplicated increase in frequency, especially if nocturnal, in a man forty-five years of age or older, who gives no history of a previous increase in frequency, is pathognomonic of the early stages of this affection. The frequency increases with the enlargement, and sooner or later becomes diurnal as well. Still later it becomes complicated by urgency and pain, and then by tenesmus, all of these depending upon the degree of prostatitis and urethrocystitis that have developed, and in some cases (especially those of an advanced type) upon the presence or absence of a calculus.

All varieties of acute cystitis cause increased frequency of micturition. If the inflammation be severe, or if it centre about the neck of the bladder, as it commonly does, there will be extreme frequency with urgency, which latter symptom may amount to a slight incontinence on occasions. There will also be pain and tenesmus, the latter sometimes amounting to strangury. As a rule, however temporary relief quickly follows the terminal pain and tenesmus.

In chronic cystitis frequency of micturition may be absent during the quiescent periods and during mild exacerbations. Urgency is rare. Unusual frequency with urgency, pain and tenesmus, denotes a sharp exacerbation. Oft-recurring exacerbations in cases with little or no prostatic enlargement furnish strong presumptive proof of the presence of a calculus in the bladder; and when such exacerbations occur in cases in which the prostate is enlarged, they indicate either that a fresh infection has taken place, or that there is a calculus in the bladder, or both. When a sharp hæmaturia accompanies the exacerbations a differential diagnosis will be required between ulceration—simple, gonorrhæal, or tuberculous,—a calculus, and a neoplasm.

When a calculus is present in the bladder, diurnal rather

than nocturnal increase of frequency is a characteristic of the condition. Micturition is usually accompanied by pain, sometimes also by tenesmus, depending upon the size of the calculus, the character of its surface, and the degree of cystitis. Thus the increased frequency may become practically incontinence. The terminal pain is referred usually to a point about an inch back from the meatus. When the calculus is small and mobile, and therefore capable of rolling against the vesical outlet, there occur sudden attacks of increased frequency, urgency, pain and tenesmus, with a minimum of cystitis. Recumbency lessens the suffering; occasionally it gives complete relief. Exercise, especially that which jolts the pelvis, aggravates the symptoms.

In pyelitis, when acute and of high grade, the frequency, urgency, pain, and tenesmus referred to the neck of the bladder, may simulate vesical calculus. Chronic pyelitis gives at most a slight increase in frequency of micturition.

The presence of a small tumor in the bladder, if it be seated at a point remote from the outlet, may not affect micturition. In a case of this character an uncomplicated hæmaturia is the only symptom that would point to the presence of the tumor. Larger tumors produce increased frequency which is in direct proportion to their size; they also produce urgency, pain, and tenesmus, all of which symptoms depend for their severity upon the location and mobility of the tumors. This applies also to polypi in the prostatic urethra.

In ulcer of the bladder, simple, gonorrhæal or tuberculous, urgency depends upon the proximity of the ulcer to the vesical neck. If it be situated within the neck, there will be more or less pain and tenesmus, sometimes initial as well as terminal, with more or less hæmaturia.

In vesical tuberculosis an otherwise unaccountable increase in frequency, diurnal and nocturnal, is an early symptom. Cystoscopy often aids in the diagnosis. Later, the presence of urgency, pain, and tenesmus, and their severity, depend upon the proximity of the lesion to the vesical neck and upon the extent of the lesion independently of its location. In advanced cases the pain and tenesmus usually are very severe and may be accompanied by hæmaturia. A negative examination for tubercle bacilli in the urine is not conclusive.

In renal tuberculosis, renal calculus, and ureteral calculus, when not complicated by cystitis, these affections may give rise to an uncomplicated diurnal increase in frequency. Renal colic, due to any one of the above causes or to movable kidney, may be accompanied by reflex increase in frequency, urgency, pain, and tenesmus.

Among the acute symptoms associated with intermittent hydronephrosis there is usually more or less increase in frequency of micturition, often accompanied by urgency, pain, and tenesmus; the severity of these symptoms depending upon the cause of the hydronephrosis. As the attack subsides and the pent-up urine is liberated, there is likely to be a slight, uncomplicated, transient increase in frequency due to the sudden increase in the quantity of the urine.

In tuberculous prostatitis the incipient stage and occasionally a more advanced stage give, as a rule, no urinary symptoms. When the disease is well advanced it causes increased frequency and more or less urgency, accompanied by terminal pain and tenesmus so sharp as to simulate vesical calculus. The diagnosis is established by exclusion and by the discovery of nodules in the prostate on digital rectal examination. A negative examination for tubercle bacilli in the urine is not conclusive.

Increase in frequency of micturition occurs as a neurosis in young and neurotic individuals, and possibly also in neurasthenic men. The increased frequency is diurnal and may become exaggerated by the large quantity of urine which these patients sometimes excrete. In some cases any attempt to postpone the act of micturition causes severe pain. The differential diagnosis between this neurosis and incipient vesical tuberculosis is sometimes difficult without the aid of cystoscopy.

In hernia of the bladder, before cystitis has developed, increase in frequency is the only urinary symptom. The pathognomonic signs are: a more or less tense, fluctuating tumor in the usual site of an inguinal hernia; its disappearance under gentle manipulation while the patient is recumbent; his ability to rise and void another volume of urine, although he emptied his bladder immediately before the reduction; and, finally, the reappearance of the tumor when the bladder is distended with fluid.

In contracted bladder the increase in frequency is as pronounced during the night as it is during the daytime. When the contraction is due to interstitial changes following long-standing chronic cystitis from any cause, or when it is due to advanced tuberculosis, progressive, or stationary, there are increased frequency, some urgency, and more or less terminal pain and tenesmus.

Two very rare conditions—a congenitally small bladder and an undeveloped bladder due to a long-neglected incontinence in childhood that has resulted in the habit of frequent micturition—give equal diurnal and nocturnal increase in frequency as the only symptoms so long as there are no complications.

In chronic lesions of the spinal cord, a degree of increased frequency, which may well be described as an irritability of the bladder, is common in the earliest stages. Later on, there occurs an increase in frequency which is dependent upon distention of the bladder.

Hesitancy or Slowness in Starting the Stream.—As a pure neurosis hesitancy is very common; it is seen in the difficulty which certain patients experience when they attempt to urinate in a hurry or in the presence of others.

In prostatic enlargement hesitancy is an early and practically constant symptom. In chronic contraction of the prostatic fibres surrounding the neck of the bladder it is equally common.

In acute inflammatory conditions of the urethra hesitancy is due either to urethral spasm as such, or to an inhibitory effect through fear of the *ardor urinae*.

Chronic lesions of the urethra—e.g., granulations or an irritable stricture—sometimes produce a momentary urethral spasm.

In acute and chronic inflammatory affections of the prostate and seminal vesicles hesitancy may result either from the slight mechanical obstruction offered or from a slight urethral spasm.

Painful diseases of the rectum—e.g., ulcer, fissure, or inflamed hemorrhoids—not infrequently produce a momentary urethral spasm.

Incontinence.—Three forms are recognized: 1. A constant, passive, more or less continuous flowing away of the urine. 2. An involuntary escape of a few drops of urine on occasions. 3. An inability to retain sufficient urine in the bladder to constitute an act of micturition, or the constant voluntary—sometimes involuntary—emptying of the bladder by the expulsion of a few drops very frequently. (The nocturnal enuresis of children is not included, as it does not come properly under the title of this article. See *Enuresis*.)

1. This first form is true incontinence. Ordinarily it occurs under only two conditions: (a) overdistention of an atrophic bladder; (b) atony of the vesical sphincters, with or without atrophy.

Prostatic enlargement is the most classic cause of overdistention with atrophy and therefore of true incontinence in a man past the age of fifty-five. The incontinence is chiefly, if not wholly, nocturnal. Filiform stricture of the urethra, if of long standing and associated with marked atony of the bladder, bears the same relation to true incontinence in younger men. Here the incontinence is chiefly diurnal, and often alternates with acute retention.

Among the diseases of the spinal cord locomotor ataxia (tabes dorsalis) and other sclerosis often cause atony of the bladder, thus permitting overdistention and true incontinence. Spastic contractions of the vesical sphincters will foster the overdistention; sensory disturbances causing anaesthesia of the region will augment the incon-

tinence. On the other hand, the reverse—viz., atony of the sphincters and hyperaesthesia—may obtain.

2. This form of incontinence presents many grades and is a symptom of several different lesions. The occasions on which it occurs are: exacerbations in the causative lesions, and any sudden unusual pressure upon the bladder, such as takes place in coughing, sneezing, jumping, or lifting a weight. The causative lesions are: chronic posterior urethritis; ulcers near the neck of the bladder, simple, gonorrhoeal, or tuberculous; vesical calculi; vesical tuberculosis, especially when affecting the neck, whether with or without ulceration; renal tuberculosis ("slight incontinence with frequency, in the absence of other lesions, is strongly suspicious of renal tuberculosis"); contracted bladder due to antecedent extreme pericystitis or interstitial cystitis; chronic prostatitis; slight atony, or "relaxation," of the vesical sphincters without atony of the bladder.

3. This is the least characteristic form of incontinence. It is merely an extreme frequency with uncontrollable urgency, and is therefore complicated by more or less pain and tenesmus. The lesions that cause it are: severe acute posterior urethritis; acute cystitis; a large rough, movable calculus, or a collection of faceted calculi, occupying the cavity of the bladder and partially distending it; a small, rough calculus, lodged in the prostatic urethra; renal calculi, causing attacks of severe colic.

Interrupted Stream.—This is also known as the "stammering stream."

The causes of this disorder operate either (1) mechanically, by intermittent obstruction, or (2) reflexly, by intermittent excitation of the vesical sphincter. Under the first class are: Prostatic enlargement; chronic contraction of the prostatic fibres surrounding the neck of the bladder; a small, rounded, mobile calculus; a pedunculate tumor; a blood clot. Under the second class are: Acute, subacute, and chronic urethritis; stricture of the urethra, both of large and small calibre; neurasthenia and neurotic tendencies.

Retention.—Confusion arises from the use of the word retention when suppression is meant. Retention of urine applies only to its discharge from the bladder, while suppression of urine applies only to its excretion by the kidneys.

Retention is due either to a mechanical obstruction, which prevents the escape of urine from the bladder, or to a diminished expulsive power on the part of this organ; this latter condition being due in turn to impaired innervation of the muscle coat, or possibly to some actual lesion of the muscle. In obstructions of long standing the retention is due to a combination of both these factors, for the hypertrophy which developed in the wall of the bladder as a result of its early efforts to overcome the obstruction finally gives way to an atrophy, the degree of which is in direct ratio to the chronicity of the obstruction.

I. Acute Retention.—The cause may be (a) organic obstruction; (b) spasmodic obstruction; (c) a combination of both; (d) a sudden impairment of the bladder function, with or without spasm of the sphincter.

(a) The following are among the more important organic obstructions: a stricture of small calibre, when inflamed by sexual and alcoholic excesses, by excessive coffee drinking, or by exposure to cold and wet; a prostatic enlargement, when acutely congested or inflamed—a condition to which it is peculiarly liable after any excesses in venery, eating, and drinking, and as a result of constipation; acute prostatitis, simple or gonorrhoeal, especially when resulting in an abscess that is pointing toward the bladder; a rupture of the urethra, complete or partial; plugging of the internal meatus, e.g., by a small, movable calculus, a pedunculate vesical tumor, or a blood clot; and, finally, periurethral abscess, especially when located in the bulbous portion. Among the rare organic obstructions should be mentioned: Acute posterior urethritis, severe acute seminal vesiculitis, tuberculous prostatitis, and papilloma of the urethra.

(b) Spasmodic obstruction—i.e., obstruction caused

by spasm of the sphincter—occurs under the following circumstances: in acute anterior urethritis, occurring either independently or in connection with an existing urethral lesion (*e.g.*, a stricture or a granular patch); when the urethra is the seat of a comparatively slight trauma, inflicted by a blow, by rough instrumentation, or by irritating injections; when there are rectal lesions, including fecal impaction and even constipation of only two or three days' standing; after operations, minor as well as major, on the urethra or on the rectum or some contiguous region, whether performed under local, spinal, or general anaesthesia; in the presence of shock, post-operative or traumatic; as a result of enforced postponement of micturition, especially if there is present any lesion of the urethra, prostate, or seminal vesicles; * in exhausting diseases, such as typhoid fever, pneumonia, peritonitis, and meningitis; in vesical tuberculosis; in pyelitis, simple, gonorrhoeal, tuberculous, or due to a calculus (the last-named occasionally causes acute retention instead of the more usual frequency and urgency of micturition); in hernia of the bladder—a rare occurrence; and, finally, in neuroses and neurotic conditions in general.

(c) A combination of organic and spasmodic obstructions is observed in severe acute posterior urethritis, when the swelling is extreme and when spasm is excited. It is also observed in severe acute prostatitis and in seminal vesiculitis.

(d) Sudden impairment of the bladder function, with or without spasm of the sphincter, may be observed in rupture of the bladder, whether intra- or extraperitoneal, and also in those injuries or diseases of the central nervous system which result in the production of a sudden hemiplegia or paraplegia, with or without coma.

II. Chronic Retention.—This is either partial or complete. Chronic partial retention results when only a portion of the urine is spontaneously voided, the rest remaining in the bladder as "residual urine." Chronic complete retention exists when all spontaneous micturition has been lost and all the urine has to be drawn by catheter.

In prostatic enlargement there is at first only partial retention. This advances to complete retention if, the true state of affairs not being recognized, the bladder is allowed to become atonic through overdistention. Thus arise the cases of chronic complete retention which have apparently assumed this character from the outset. An intercurrent acute retention is often the first symptom for which the patient seeks advice, he having disregarded the symptoms of the partial retention.

The remarks made in reference to prostatic enlargement in a preceding paragraph apply with equal appropriateness to chronic contraction of the fibres surrounding the neck of the bladder. This chronic contraction, however, is less frequent than prostatic enlargement, and consequently it gives rise less often to chronic complete retention.

In filiform stricture of the urethra the chronic retention is only partial; it will disappear after appropriate treatment of the stricture unless the latter has been neglected for many years.

In chronic prostatitis, in tuberculosis of the prostate, and in vesical tuberculosis a small quantity of residual urine is an almost constant objective symptom.

As further causes of chronic retention may be mentioned: habitual failure to empty the bladder completely by reason of hurry or indifference; and frequently repeated prolonged postponement of micturition, thus causing frequent overdistention.

While the retention which originates in some chronic lesion of the spinal cord is only partial, it is nevertheless characterized by a large volume of residual urine—from five to twenty ounces. In the mild cases the amount of the residual urine will fluctuate even under the best conditions, often falling to two ounces. On the other hand,

the amount is fairly constant in the more advanced cases, and the retention is associated with frequency, or with incontinence, or with both.

James Pedersen.

MOUTH, DISEASES AND INJURIES OF.—**I. STOMATITIS.**—"This word, which from its derivation signifies inflammation of the mouth, is held to include inflammatory affections of the cavity of the mouth as far back as the soft palate. Any abnormal condition of an inflammatory character which involves the gums, the tongue, or the inner surface of the cheeks, is included, therefore, under the designation of stomatitis. Experience shows that there is little tendency toward limitation to any one of these structures—usually the entire cavity of the mouth partakes of the diseased condition.

"The affections included under this name are, in great part, limited to the age of childhood. Adults are never the subjects of certain forms of the disease, and seldom suffer from any variety of it, save as part of some other morbid condition. Not infrequently, however, stomatitis is nothing more than a part of such general condition. Diphtheria sometimes involves the mouth as well as the tonsils, pharynx, and palate; inflammation, with pustulation in the mouth, may occur in smallpox, varioloid, and varicella; facial erysipelas often presents an inflamed condition of the mouth; measles, Rôtheln, and syphilis are accompanied by characteristic mouth affections; and many drugs, such as mercury and iodine, in addition to the mineral and other stronger acids, produce an abnormal condition." (From former edition of REFERENCE HANDBOOK.)

It must be remembered that in children there is a tendency to put anything and everything—all germ-laden—into the mouth; hence one reason why stomatitis is so much more common at that age. The troubles incident to the period of dentition have also a causal relation to stomatitis.

As remedies for stomatitis in general, the following have been used. As mouth washes, in the form of solutions: Potassium permanganate, gr. ij. to ʒi.; potassium chlorate, gr. x.-xx. to ʒi.; boric acid, saturated solution; carbolic acid, one-per-cent. solution; hydrogen dioxide, 15 vols. per cent.; silver nitrate, gr. x.-xx. to ʒi. Also the solid stick of silver nitrate may be employed; and potassium chlorate may be given internally in doses of gr. v.-vij. q. 4 h.; in the case of children, however, the latter remedy must be used with care. Tonics of iron, quinine, nux vomica, and cod-liver oil are required. The diet must be liquid, either warm or cold, and must be generous and sufficient; chipped ice and iced water are acceptable to the patient. The mouth must be regularly washed or, if that is not possible, sprayed. If the gums are spongy, they should be painted with tincture of myrrh.

2. CATARRHAL STOMATITIS.—(*Synonyms:* Acute stomatitis, Erythematous stomatitis, Pultaceous stomatitis, Simple stomatitis, Superficial stomatitis.)

Etiology.—It most commonly occurs in infants and children, but it is also found in adults. The most common cause is an irritant either chemical or mechanical, such as overheated or too highly spiced food, acids, alkalies, very hot beverages, broken or carious teeth, and the excessive use of tobacco or alcoholic drinks. In the case of infants irritation caused by a coral, by difficult dentition, by a poorly developed or unclean nipple, or by a feeding bottle which has not been properly cleansed, may produce stomatitis. An excess of sugar or starchy food, and also exposure to cold, are causative factors in some cases.

Symptoms.—These are the classical symptoms of inflammation: redness, first in patches, later more general; swelling, chiefly of lips, cheeks, gums, and tongue, the latter often showing the impression of the teeth; disordered secretion—in the adult the mouth is at first dry, later there is an increased flow of saliva with secretion of considerable mucus; at the same time the breath is fetid, and in children there is dribbling accompanied with considerable tenderness, so that the infant refuses to nurse or

* In these cases the spasm is usually of short duration, and it is rarely found necessary to resort to the use of the catheter in order to secure relief for the patient.

to allow the mouth to be cleansed. In adults the pain is as a rule slight, though it may be considerable, and, in conjunction with the dryness of the mouth seen in the early stages, renders mastication difficult. The disorder usually lasts about a week. In this form of stomatitis there is no ulceration.

Prognosis is good in acute cases, but infants are liable to suffer from inanition owing to the pain experienced in taking food. In chronic cases, generally due to alcohol or tobacco, the offending substance must be withdrawn.

Treatment is chiefly hygienic; whenever possible the causes must be removed and strict cleanliness insisted upon. In mild cases mouth washes of borax, of potassium chlorate, or of sodium bicarbonate may be useful; in the severer forms silver nitrate in one-per-cent. solution should be applied. At the same time general treatment in the shape of tonics and salines must not be overlooked. In infants the feeding apparatus must be kept scrupulously clean.

3. **CROUPOUS OR MEMBRANOUS STOMATITIS** is an inflammation of the mouth with the formation of a false membrane of a yellowish-white or grayish-white color. The disease may be diphtheritic or it may be due to gonorrhœa or syphilis; it is also caused by extremes of temperature (as frost-bite) and by chemical irritants. This form of stomatitis is much the same as diphtheria, but without the Klebs-Loeffler bacillus. The pseudo-membrane is apt to ulcerate and become detached from the subjacent tissue which then shows marks of erosion.

Treatment.—If the inflammation is due to diphtheria, give antitoxin; in most other cases the treatment is the same as in other forms of stomatitis, and consists of good food, proper hygiene, antiseptic and astringent mouth washes, tonics, and stimulants.

4. **ULCERATIVE STOMATITIS**.—(*Synonyms*: Fetid stomatitis, Phlegmonous stomatitis, Stomacace, Putrid sore mouth, Phagedenic gingivitis.)

This form of stomatitis is a serious condition in which there is a superficial necrosis of the mucous membrane of the mouth, with subsequent ulceration.

Etiology.—The disease is probably caused by a micro-organism, though none has as yet been isolated. It is generally found in children between the ages of four and fourteen; it may be epidemic, and is apt to accompany or follow improper feeding, infectious diseases, also poisoning by mercury, arsenic, lead, or phosphorus. Unhygienic surroundings and any local irritations are potent factors in this as in the other forms of stomatitis.

Symptoms.—The gums, of the lower jaw chiefly, are spongy, painful, swollen, and bleed readily; later on, the cheeks and lips become affected. The gums also recede from the teeth, which become loosened and may fall out; ulcers may also occur round the sockets of the teeth, and a purulent fluid forms between the gums and the teeth, as well as between the teeth. There are profuse salivation, very fetid breath, and swelling of the neighboring lymph glands. In chronic cases the periosteum of the lower jaw becomes involved, and areas of necrosis ensue. There is great debility, and nausea and diarrhœa, caused by swallowing the profuse fetid saliva, are also apt to be present.

Treatment is on the same lines as in other forms of stomatitis. On account of the disagreeable odor of the breath the patient should be isolated. Mouth washes are required, but in case potassium chlorate is used care must be taken that no untoward results occur, particularly in children. Hydrogen peroxide or dioxide makes an admirable mouth wash.

5. **BEDNAR'S APHTHÆ**, also called *Plaques pterygo-diennes*, or *aphthæ of the palate*, is a variety of ulcerative stomatitis. It is sometimes of traumatic origin, being due to pressure. It occurs generally in bottle-fed children who have unhygienic surroundings and are badly cared for, and is caused by the pressure on the hard palate of an artificial nipple or of the nurse's finger, or of a swab used in cleaning the child's mouth. But in breast-fed children it may also be found; it is then caused by the pressure of the infant's tongue on the thin mucous mem-

brane, during the act of nursing. As a rule the affection is of a mild character, and is found on the hard palate near the alveolar process, but in badly neglected cases the ulceration may be both deep and extensive. In mild cases no special treatment is required beyond the removal of the cause; while in more severe cases a five-per-cent. solution of silver nitrate should be applied.

6. **APHTHOUS STOMATITIS**.—(*Synonyms*: Follicular stomatitis, Vesicular stomatitis, Herpetic stomatitis, Aphthæ, Canker.)

In this form of stomatitis, which is more common than the catarrhal variety, the mucous membrane of the mouth is hyperæmic and is characterized by grayish or yellowish vesicles which are liable to ulcerate, and are chiefly found on the margin and frænum of the tongue, and on the cheeks; also on the inner surface of the lower lips, near the junction with the gums.

Etiology.—It is probably due to some specific germ, but none has yet been isolated. It is found most commonly in children, and, if not idiopathic, is due to improper food, indigestion, one of the fevers, lack of hygiene and general uncleanness of the mouth.

Symptoms.—The child is fretful on account of the pain; dull and feverish; the mouth is hot; the saliva flows freely and may irritate or excoriate the chin and neck. The ulcers described above are surrounded by red areolæ and bleed readily if any attempt is made to remove the grayish-white base. The process lasts about a week.

Prognosis is good. The sores may be treated with silver nitrate; local washes of potassium chlorate or potassium permanganate should be used; food, tonics, and stimulants are required.

7. **PARASITIC STOMATITIS**.—(*Synonyms*: Mycotic stomatitis, Stomatomycosis, Thrush, Muguet, Soor.)

Thrush is one form of parasitic stomatitis, but it is the most important variety. The disease is due to a vegetable parasite, and consists of white flake-like patches on the mucous membrane of the mouth and tongue. These patches consist of epithelium, leucocytes, and the spores and filaments of a fungus. The fungus or mould has been described as *oidium albicans*, *saccharomyces albicans*, *oidium lactis*, *mycoderma vini*, and *monilia candida*. The fungus displays remarkable polymorphism, having a great tendency to spore formation in a solid medium, and to filament formation in a liquid medium. The fungus tends to grow rapidly, particularly upon an unclean surface. The spores lodge between the epithelial cells; then separating the different layers and destroying the superficial layer they penetrate down into the connective tissue. The disorder is apt to become epidemic in institutions where there are many children, being transmitted by unclean feeding apparatus. The spots or patches look like curdled milk, but are covered with epithelium and are readily removed without bleeding, being thus differentiated from aphthous or follicular stomatitis.

Etiology.—The disorder is found generally in childhood, and occurs in the debilitated or uncleanly, more particularly in bottle-fed infants. It is apt to follow catarrhal stomatitis; and the growth of the fungus is favored by mouth breathing and by the restricted movements of the tongue which are necessitated by many forms of stomatitis.

Symptoms.—The symptoms are as a rule slight and much like those of catarrhal stomatitis. The saliva is acid and decreased in quantity; and the mouth is apt to be dry.

Treatment, as in other forms of stomatitis, consists in absolute cleanliness, the employment of mouth washes of an antiseptic character, the observance of a proper hygiene, and the administration of good food, tonics, and stimulants.

8. **GANGRENOUS STOMATITIS**.—(*Synonyms*: Noma, Cancrum oris, Water cancer.)

This is an uncommon but very formidable complaint, and is almost invariably found in young children. It is favored by poor hygienic conditions, lack of food, and general enfeebling diseases. It may follow an ordinary ulcerative stomatitis, but the two conditions are very

different. Probably some micro-organism is the cause of the disease, but so far it has not been isolated. Cancrum oris must not be interpreted as an ordinary gangrene of a local character, for the blood supply of the face is far too good to allow of such a supposition. Characteristics of this disease are: (1) that it begins on the inside of the cheek; (2) that it is almost always unilateral, though cases have been reported in which both cheeks were attacked; (3) that it perforates the whole thickness of the cheek; and (4) that it is rapidly fatal. At first there will be observed a small red swelling on the inside of the cheek, often opposite the opening of Stenson's duct. This small swelling gives place to a large, rapidly growing ulceration and is followed by gangrene. The destructive process begins from within and works outward. The whole thickness of the cheek is soon involved; it becomes brawny, and the outside is red and glazed; perforation soon occurs. The breath is fetid, the teeth fall out, the jaw becomes necrosed, and the whole process is marked by the extraordinary rapidity with which it advances, a rapidity so great that in from one to two weeks the patient dies either from exhaustion or from pyæmia. "The intelligence remains generally undisturbed, and the little patients do not seem to be greatly alarmed, but rather apathetic. The temperature and respiration become influenced principally because of, and in proportion to, the inflammation of the lungs, which is frequently a precedent and concomitant condition. This associated pulmonary inflammation is, however, never of the sthenic type of simple acute lobar pneumonia." (From former edition of REFERENCE HANDBOOK.) "Diagnosis in the later stage is rendered unmistakable by the ulcer, nodule, slough, and perforation. The early stage is to be distinguished from malignant pustule (anthrax). The latter begins as a pustule upon the outside of the cheek, often at the site of an abrasion; it is far more common in adults, and the anthrax bacillus is discoverable in the pustule and blood." (Thompson's "Practical Medicine.") There is very little pain, but much prostration, and generally there are nausea and diarrhoea.

The prognosis is bad; different writers place the death rate at between eighty and ninety-five per cent.

Treatment to be of any use must be vigorous and early. Free extirpation or the application of the cautery should be early resorted to; there should be frequent applications of hydrogen dioxide, and tonics and nourishing food should be administered every two or three hours.

9. MERCURIAL STOMATITIS. — (*Synonym*: Mercurial ptyalism.)

This is an inflammation of the mucous membrane of the mouth and gums, due to the use of mercury; it is rarely found in syphilitics.

Symptoms.—The patient complains of a metallic taste, tenderness of the gums which are also unusually red, and increased flow of saliva; the tongue becomes swollen and there is difficulty in both mastication and deglutition. The salivation is apt to be extreme; and the odor of the breath is most offensive.

Treatment.—Those working in mercury should cleanse both mouth and teeth frequently; and those taking the drug should at once discontinue its use. The best remedies are salines, alkaline drinks, and atropine to arrest the flow of saliva. During convalescence tonics will be required.

10. PTYALISM, or SALIVATION, and XEROSTOMIA have been described in Vol. VII. of the REFERENCE HANDBOOK, under the heading *Salivary Glands, Diseases of*; it only remains here to outline the treatment of the former condition. When ptyalism is produced by the administration of mercury, as is (or was) generally the case, the use of that drug should be discontinued, the mouth should be washed with astringent lotions such as alum or potassium chlorate, and potassium iodide should be given internally. Mercurial salivation can often be prevented or diminished by devoting proper care and attention to the condition of the patient's mouth and teeth; it has been asserted that the administration of small doses of

potassium chlorate in conjunction with the mercury will also lessen the likelihood of salivation. In ptyalism from other causes the tincture of belladonna has been recommended in doses of m x. t.i.d.

11. ANGINA LUDOVICI, or Ludwig's angina, is the name given to an infective inflammation of the floor of the mouth, and of the cellular tissue beneath the deep cervical fascia. It generally begins in the submaxillary glands, and is due to an infection with one or more varieties of the pus-producing bacteria—probably the streptococcus pyogenes—and is accompanied by much swelling and infiltration of the mouth, tongue, throat, and neck. There are severe pain and dyspnœa, the latter being often caused by œdema of the glottis. The patient finds great difficulty in opening his mouth, in talking, and in masticating and swallowing his food. Sloughing of the soft parts is apt to ensue and is called *cynanche gangrenosa*.

Prognosis is not good.

Treatment consists in the employment of antiseptic measures and in making a prompt and free incision into the involved tissue, generally in the median line. Tracheotomy may be demanded for œdema of the glottis. Tonics and nourishing food are indicated. (See also Vol. VI., p. 593.)

12. PERLÈCHE is a contagious disorder consisting of fissures at the angles of the mouth. The trouble is found chiefly in children, and is very painful. It is probably caused by a micro-organism; Le Maistre reporting a streptococcus, and Raymond a variety of staphylococcus in connection with this disorder. It lasts for from ten to twenty days, and is bilateral, beginning at the angles of the mouth, and spreading along the border of the lips. The lips swell and are painful, and are apt to ulcerate. The skin around the mouth is not often attacked, but the mucous membrane is involved and the epithelium becomes white and sodden and is then desquamated. Pain and itching are present, and the child licks the parts to relieve the pain and burning; hence the name, from the French *perlécher* (= to lick). The disease is spread by drinking-vessels. Treatment consists in cleanliness and the use of astringent lotions of alum, copper sulphate, or even nitrate of silver. A dusting powder of bismuth subnitrate may be used; and, as a prophylactic measure, children should have their own cups to drink out of.

13. RIGA'S DISEASE occurs as a gray ulcer with an irregular border situated under the tongue, near the frænum. It appears about the period of first dentition, and lasts for a variable period, usually about a year. It has been found almost epidemic, certainly endemic, in Southern Italy. Its origin is most likely traumatic. The treatment is that of catarrhal stomatitis.

14. SALIVARY CALCULUS may occur in the excretory duct of any of the salivary glands, but is most frequently found in Wharton's duct. It consists of phosphate and carbonate of calcium together with sodium chloride and magnesium. After such a concretion is formed, it may either remain in the gland, or be discharged through the duct, or it may obstruct the duct. In the two former conditions it gives no trouble, but in the last case it gives rise to pain and swelling of the gland with which it is connected; the swelling is always increased on taking food. Careful palpation along the course of the duct will help in making a diagnosis; and, except in mumps, pain and swelling in a salivary gland should always suggest salivary calculus.

Treatment consists in making an incision into the duct, either in the distended portion only, or in its whole length from the outlet to the obstruction. If left untreated the duct may burst, with formation of a salivary fistula.

15. SALIVARY FISTULA is an abnormal opening of the duct of a salivary gland, and may be either internal or external, according as it opens on the inside of the mouth or on the outer surface of the cheek. Such a fistula is due to wounds of the duct, or to a rupture of the duct from suppuration or calculi. The parotid gland is the one most commonly affected. Internal salivary fistula is of comparatively little consequence, as the saliva flows into

the mouth. But in external fistula the flow of saliva on the cheek causes considerable discomfort.

Treatment.—If a calculus is present it must be removed. Then find the internal opening of the duct, and see if it is patent; if it is not patent, an artificial internal fistula must be made; and the edges of the external fistula can be touched with a caутery or pared, and closed with a twisted suture.

16. **TONGUE-TIE** is practically a congenital shortening of the frænulum linguae. The tongue cannot be protruded beyond the teeth; and suction and, later, articulation are interfered with. The proper treatment is division of the frænum, generally on the notched shield which forms the handle of a grooved director. Care must be taken to avoid wounding the ranine arteries. Blunt-pointed scissors should be used, and the points directed toward the floor of the mouth and away from the under surface of the tongue. Often the frænum is simply nicked with the scissors and the operation completed with the finger nail.

17. **PYORRHEA ALVEOLARIS**, or Rigg's disease. In this condition there is found a shrinkage of the gums and alveolar border, together with separation of the gums from the teeth, which become loosened and may fall out. It is due to an inflammatory condition of the gums combined with bacterial infection and an excess of tartar. General cleanliness is indicated, with removal of the tartar; antiseptic and astringent mouth washes and general tonics should also be prescribed. Treatment may have to be continued for a long time as the condition is often intractable; and the patient may expect to lose some of his teeth.

18. **ALVEOLAR ABSCESS** is the result of inflammation and suppuration in connection with the fang of a carious tooth. It may occur in either jaw. Pus forms in the socket of the tooth and either finds its way out by the side of the tooth or through the gums, in which latter case it is called a gumboil or parulis; occasionally it strips the periosteum from the bone and forms an abscess of large size, and may even produce necrosis of the jaw. The first indications of the trouble are pain and a feeling as if the tooth were a little longer than normal. If the abscess is allowed to remain, there may be severe constitutional symptoms. Incision is indicated, and if it be delayed the tooth becomes loosened and exfoliation of the periosteum with necrosis may occur. In the upper jaw pus from a neglected alveolar abscess may burrow into the antrum of Highmore and set up suppuration there, or it may discharge by way of the nose. In the lower jaw the pus may travel downward and point and burst in the neck.

Treatment consists in disinfection of the mouth, incision of the gum, and extraction of the tooth. As a prophylactic, children should be taught to use a tooth-brush, and their teeth should be regularly attended to by a competent dentist.

19. **EPULIS**.—This term is applied to a tumor growing from the fibrous tissue of the gum or from the alveolar periosteum. The name is derived from *ἐπι* and *ὄϊλον*, and means literally a tumor situated "on the gum." There are two varieties: the simple or fibromatous, and the malignant or myeloid. They generally attack the lower jaw.

Simple or fibromatous epulis appears as a rounded, smooth mass, sometimes lobulated or sessile; it is firm or elastic to the touch, and of a color varying from pinkish to deep red. It is generally due to carious teeth and is more apt to be formed on the outer border of the gums, though it may appear between two teeth, causing more or less displacement, and also on the inner surface of the gum. It is covered with epithelium, and may contain a few spicules of bone derived from the maxilla. The presence of the latter is much more common in the malignant or myeloid variety.

Treatment consists in the free removal of the tumor together with any teeth, stumps, or bone that may appear to have some causal relation to the growth. It is well, therefore, to extract a tooth on each side of the epulis, to cut through the whole thickness of each al-

veolus vertically with a small saw, and then finally to join these incisions at their lower ends by a horizontal incision made with a chisel. Thus the continuity of the jaw will remain notwithstanding the fact that a quadrangular piece of bone has been removed.

Malignant or Myeloid Epulis.—This is really a myeloid sarcoma and springs from the alveolar process. The chief distinction between these two varieties is pathological; the clinical picture being much the same as in the simple variety, except that the mucous membrane covering the tumor is more apt to ulcerate, and there is always a connection with the underlying bone. The treatment, too, is the same, only the malignant variety sometimes requires very energetic and radical treatment.

20. **WOUNDS AND INJURIES OF THE MOUTH** have, for the most part, the same features as are presented in wounds and injuries elsewhere. The blood supply of the mouth being particularly abundant, there is apt to be profuse hemorrhage, but this same abundant blood supply causes the processes of repair and healing to be very rapid. Hemorrhage from the mouth is due to wounds, injuries, purpura, biting the tongue, plethora, scurvy, and the hemorrhagic diathesis; it is best controlled by the application of cold or pressure. In slight cuts of the lips a little cotton soaked in collodion makes a good protective and also stops the bleeding. In wounds of the mouth we must remember that the buccal cavity always contains bacteria capable of producing infection, and therefore asepsis is not attainable; but antiseptic mouth washes should be used as frequently as possible.

21. **BURNS AND SCALDS OF THE MOUTH**.—These are generally caused by accident, and are due to hot liquids introduced into the mouth, to chemicals (acids and alkalis), or to inhalation of hot air or steam. They are most commonly met with in children, owing to their greater liability to drink out of the spout of a kettle or teapot. Adults are more likely to suffer in explosions, under which circumstances they may inhale steam or ignited gas. The inside of the mouth and pharynx are involved, and edema of the glottis is a probable complication. The symptoms are intense burning pain, dyspnoea, suffocating cough; the lips and mucous membrane of the mouth are either white, sodden, puffy, and blistered, or the mouth may escape and show little or nothing of the hurt. In this latter event the glottis may be scalded, when the edges of the epiglottis will be scorched and the larynx also involved.

Treatment is the same as that for burns in other parts of the body: (1) *constitutional*, to combat shock and to keep up the patient's strength; and (2) *local*, in the form of mild antiseptic mouth washes and cool mucilaginous drinks. For edema of the glottis tracheotomy may be required. There may be cicatricial contractions resulting in great deformity, and, for the relief of this deformity, extensive plastic operations are often performed.

22. **ERRORS OF DEVELOPMENT**.—The chief of these are harelip and cleft palate, both of which are considered in other parts of the REFERENCE HANDBOOK. Among the other defects, of which mention may be made here, are the following:

Astomia, or absence of the mouth; this, of course, is incompatible with life.

Atresia oris differs from the above in that there is a buccal cavity, but no external opening. This defect is generally combined with other errors of development. The line of the closure is more or less apparent, and the membrane may be thin or tough and dense. As in similar conditions elsewhere incision is required, but care must be taken lest the freshened edges grow together again.

Microstomia, or congenitally small mouth, is a milder form of atresia oris, and is due to the fact that the parts that form the lips have fused to a greater extent than normal, thus causing stenosis of the buccal orifice. The mouth may be so small that the infant cannot nurse. In such a case it must be enlarged sufficiently and the mucous and cutaneous borders stitched together.

Macrostomia, or congenitally large mouth, is gene-

rally unilateral, and is said to occur more frequently in females. It is found in connection with other developmental errors, and is usually due to the non-union of the mandibular and maxillary processes, or to the persistence of the lachrymal fissure. The treatment consists in paring and uniting the edges of the cleft sufficiently to reduce the mouth to normal dimensions.

R. J. E. Scott.

In preparing this article use has been made of the following: The former edition of the REFERENCE HANDBOOK; Ziemssen's "Cyclopædia"; Reynolds' "System of Medicine"; Pepper's "System of Medicine"; Albutt's "System of Medicine"; Keating's "Cyclopædia of the Diseases of Children"; Thompson's "Practical Medicine."

MULTIPLE (CEREBRO-SPINAL) SCLEROSIS.—(Synonyms: Disseminated sclerosis; Insular sclerosis.)

DEFINITION.—This disease may present manifold symptoms, the most common of which are paresis, with muscular rigidity and exaggerated tendon reflexes as in spastic paralysis, tremor brought on by voluntary movements, nystagmus, scanning speech, amblyopia, apoplecticiform attacks, and impaired intellect. The anatomical basis of the disease consists of disseminated patches of sclerosed tissue in various parts of the central and peripheral nervous systems.

ETIOLOGY.—An hereditary influence has been traced in a few instances. Charcot states that the disease occurs most frequently in females, but a number of other observers do not concur with him in this view. It occurs most frequently between the ages of fifteen and thirty; occasionally in young children; rarely, if at all, after forty.

Traumatic influences, such as blows on the head, concussion of the whole body, exposure, hardship, overwork, and profound emotional disturbance, may all be mentioned as occasional exciting causes. In a number of instances the disease developed after the existence of an acute disease, typhoid fever, variola, etc.

SYMPTOMS.—The area of diseased tissue may be located in any part of the nervous system and there may be quite a number of affected areas. Furthermore, the disease may be of various degrees of severity, and the symptoms, which are but the expression of the locality and intensity of the disease, may make the most varied clinical pictures. There may be an entire absence of symptoms of disease of the nervous system, although nodules of sclerosed nerve tissue are found post mortem; or the disease may simulate various different organic or functional nervous diseases. But, nevertheless, the sclerosis seems to have a predilection for certain parts of the nervous system, and we find, accordingly, in many cases similar, and almost characteristic, clinical manifestations.

A cerebral and a spinal form of multiple sclerosis are sometimes spoken of, but usually both brain and cord become involved in the disease, though it may have been present in the one some time before it developed in the other. Generally the spinal cord is first affected.

The disease usually begins very insidiously and is slow in its progress; in rare instances it has an abrupt beginning, perhaps is ushered in by an apoplecticiform attack. The earliest symptoms may be of cerebral origin, such as headache, vertigo, ataxic gait, and slight psychic disturbances; or there may be a slight tremor in one or both hands; but more frequently the symptoms are those of spastic paralysis.

At first there is weakness of one leg, then of both, attended by some difficulty in walking. Gradually, with increasing paresis of the limbs, there appear muscular rigidity, especially brought on by active or passive movements, exaggerated tendon reflexes, spastic gait, and, finally, rigid contractures of the limbs. The paresis, and, to a less extent, the muscular rigidity, etc., at a later period affect the upper extremities, and to these is subsequently added another motor symptom—one of the most prominent and characteristic of this disease—the so-called intention tremor, *i. e.*, tremor during the performance of a voluntary act. Before it is otherwise

noticeable, it may be observed in the handwriting or other delicate movements of the fingers, especially if the act is slowly performed. The writing, if carefully observed, will be seen to be full of small indentations which occur with great regularity, indicating that the tremor is rhythmical. When the tremor is well marked any voluntary movement will cause it to appear, and it may be seen to some extent during rest. A common method of eliciting the symptom is to ask the patient to put a glass of water to his lips. The tremor increases and the oscillations of the hand are greater as the latter approaches the mouth. The trembling may become so violent that all the water is thrown out of the glass. When the patient is sitting quietly either there is no tremor, or slight movements of the head and trunk may be observed. If he now perform a voluntary act, as lifting an arm, the tremor in the head and trunk increases at the same time that there is tremor of the acting member. When he attempts to walk there may be such violent tremor of the limbs and trunk as to make walking, or even standing, almost impossible. On the other hand, when the patient lies down and every part is well supported no tremor appears. None is observed during sleep. It is increased by emotional excitement.

All the voluntary muscles may be thus affected, the head as well as the trunk and limbs. Tremor in the face is less commonly seen, though there may be irregular movements, choreic in character.

The distinctive features of the tremor are that it is rhythmical, and that it occurs only with muscular efforts. A very few cases have been reported in which it continued even in rest, but such cases are exceedingly rare. The tremor is not found in all cases. It probably depends on the locality of the disease. It also disappears in any part when the latter has become completely paralyzed.

The tremor can usually be easily distinguished from that of other diseases. In paralysis agitans, in the beginning (and it is only then that the two diseases could easily be confounded), only a few fingers are affected, and the oscillations are fine and very rapid. At the same time the tremor has somewhat the character of coordinated movements. Thus the movement of the thumb upon the fingers has been likened to that of counting money, rolling pills, etc. The tremor of multiple sclerosis is large and coarse, with no appearance of coordinated action. In paralysis agitans, furthermore, the tremor is, to some extent, controlled by voluntary movement, and increases with rest, and the head is very rarely affected. When the tremor is violent it may have the appearance of the movements of chorea. But the latter occur during repose as well as during volitional acts, and they cause an intended movement to be made very irregularly; on the other hand, in multiple sclerosis the general direction of any movement is maintained, but the line of movement is an undulating one, the undulations playing equally up and down along the central line of direction.

The next two symptoms seem to be similar in character to the tremor. The first is nystagmus, a very common symptom, and of value in diagnosis. When not otherwise noticeable, it may be made manifest by movements of the eyes, strong convergence, or forced movements in some direction. The other symptom is scanning speech. Other changes of speech are sometimes present, but this is the most common and most characteristic, and, therefore, of high diagnostic value. The speech is slow and dragging, each syllable being pronounced separately as in the slow scanning of verse, and, therefore, termed scanning speech. If the patient attempts to speak more rapidly, his words are likely to be so jumbled together as not to be at all understood. The voice is monotonous to the highest degree. There is often tremor of the lips at the same time, and, on laryngoscopic examination, there has been found to be diminished tension of the vocal cords.

Other ocular symptoms besides nystagmus are frequently found. Double vision, due to paralysis of some

of the external muscles of the eye, occurs, just as in locomotor ataxia, either as a transient symptom at an early period of the disease, or as a permanent condition at a later stage. Amblyopia is also a common symptom. Generally there is only impaired vision, not complete blindness. The ophthalmoscope reveals, in these cases, a discoloration of the discs, due to a degree of atrophy of the optic nerves.

Headache and vertigo are often present, both in the early and in the later stages of the disease. The vertigo often occurs in paroxysms. Occasionally it is due to the double vision, but more frequently it is quite independent of the latter condition.

The mental symptoms often play an important rôle. Sight psychic symptoms may be manifested in the beginning of the disease if the latter first affects the brain, but the graver symptoms are, usually, late manifestations. Change in disposition, irritability, loss of self-control, a tendency to laughing and crying, are common conditions. A certain impairment of intellect—weakened memory, a degree of apathy, etc.—is also not uncommon. But a high degree of dementia is rare. It is likely to occur only when the disease begins at an early age and there is arrested development of the brain, or when the pathological process is very acute. Different forms of insanity are sometimes observed, most frequently melancholia, occasionally delusional insanity.

Apoplectiform seizures, like those seen in general paralysis, are important symptoms. They occur, according to Charcot, in one-fifth of all cases. After slight prodromal symptoms, headaches, etc., coma develops within a few hours, the temperature rapidly rises, often reaching 104° or 105° F., and at the same time the face is flushed and the pulse rapid. Hemiplegia, with flaccidity of the paralyzed muscles, is soon observed. Within a day or two consciousness returns, the temperature falls, and, within a comparatively brief period, the paralysis disappears. Such attacks may occur every few months, or very rarely. They usually leave the patient in a permanently worse condition, thus marking the progress of the disease. Sometimes the patient dies in the attack. These seizures are very much like those of apoplexy, but post-mortem examinations reveal no anatomical basis for them.

In the foregoing have been given the most common symptoms of multiple sclerosis, those found in the majority of cases. But, on account of the distribution of the diseased areas, various other symptoms may be manifested. Thus the disease may attack the posterior columns of the cord, and ataxia, pain, anaesthesia, paræsthesia, etc., will be present; or it may involve the gray matter, when atrophy and paralysis of muscles will ensue. Or the disease may involve the whole thickness of the cord and produce the symptoms of transverse myelitis. When the posterior as well as the antero-lateral columns are affected, many of the appearances of spastic paralysis are likely to be absent, especially the exaggerated tendon reflexes. Symptoms referable to the bladder and to the rectal and genital functions are also likely to appear. If the disease involve the nuclei of the facial, hypoglossal, and pneumogastric nerves, the ordinary symptoms of labio-glosso-laryngeal paralysis will be manifested, and various local cerebral symptoms may appear, according to the location of the foci of disease.

The course of the disease is a very chronic one. Charcot has divided it into three stages—a division applicable to those cases which present the common clinical picture.

The first stage is from the beginning of the disease to the period of complete disability from paralysis and contractures of the limbs. This stage may last for from two to six years or longer. The symptoms are very slow in their progress. They begin as spinal or cerebral, but both sets of symptoms appear before this stage is terminated. There is often an arrest of the symptoms, or even improvement, which indefinitely prolongs this stage, and may give rise to delusive hopes of complete restoration to health.

The second stage, that of the fully developed disease,

may last also for from two to six years. There seems to be little change in the patient during this period, and, though entirely helpless, he seems not to suffer in general health.

The third stage is that of decline. The general health is affected, there are loss of appetite, wasting, etc. Cystitis, decubitus, pyæmia, etc., may hasten the end. Or the latter may be due to an increase in the bulbar symptoms, or to an apoplectiform attack. More frequently a fatal termination is caused by an intercurrent affection—pneumonia, typhoid fever, or, above all, phthisis.

The average length of the disease is from six to eight years. In rare cases it terminates in a year or two; occasionally it lasts twenty years.

MORBID ANATOMY.—The pathological changes can usually be seen by the naked eye. They consist of numerous patches or nodules of sclerosed tissue scattered throughout the nervous system. The nodules vary in size from merely microscopical proportions to an object as large as a chestnut or larger; they are rounded or irregular in shape, and may often be seen on the surface as slight prominences or depressions, but are found in larger number when sections of the brain and cord are made. Their color is mostly of a gray or reddish-gray; they are translucent, and have a firm, often cartilaginous, consistence. Many of the nodules are of the same color as the surrounding tissue, and are only distinguished by their consistence. In rare instances a few may be softer than the normal tissue, probably indicating recent disease; most of the nodules, on the other hand, are firmer than the normal tissue, doubtless being of very old standing, for such cases come to the post-mortem table only after the disease has existed a long time. The nodules seem to be quite distinctly circumscribed, but the microscope reveals the fact that they merge imperceptibly into the healthy tissue. They are also quite distinct, as a rule, though occasionally they blend into one another. In rare instances there has been found, in both the brain and the spinal cord, a diffuse sclerosis which, to some extent, has united the scattered nodules. On the other hand, secondary degeneration seems rarely, if at all, to develop from the disseminated disease.

The number of nodules found in a single instance may be very small, or may run into hundreds. Their distribution in the cord is very irregular. In some sections they may be found in the anterior, in others in the posterior, columns; in still others in the gray matter, or they may involve all these parts in the same section. Usually a large number of nodules are found in the medulla, pons, and crura cerebri. It is very rare that these parts are found free from disease. In the hemispheres the walls of the ventricles, corpus callosum, and centrum ovale are favored seats of the disease. In the latter two localities the nodules are often quite large. Usually nodules are also found in the large ganglia, while the cortex generally escapes. But few nodules are, as a rule, found in the cerebellum, and these in the central white matter. Similar nodules may be found in the nerves, most frequently in the optic nerves, but occasionally in the hypoglossal, the nerves of the eye, and the roots of the spinal nerves.

The microscopical appearances are those of interstitial myelitis. The nodules are mostly new connective tissue composed of very fine wavy fibrillæ. But in this new tissue the axis cylinders of the nerve fibres can usually be found in large numbers, though their medullary sheaths have disappeared. This is especially true of the nodules in the spinal cord.

At one of the meetings of the Society of German Naturalists and Physicians, Adamkiewicz expressed the opinion that the disease is not interstitial, but develops primarily in the nervous tissue, beginning in the medullary sheaths of the nerves. He bases his opinion upon results obtained by a new method of staining the nervous tissue. His view is altogether at variance with that formerly held, and may be looked upon with doubt, at least until further corroboration is forthcoming.

MORBID PHYSIOLOGY.—Many of the symptoms are

easily explained by the lesions found: psychic symptoms by disease of the hemispheres, bulbar symptoms by lesions of the medulla, muscular atrophy by lesions in the anterior cornua, anæsthesia and ataxia by disease of the posterior columns, spastic paralysis by disease of the antero-lateral columns—in some instances cerebral lesions may produce the same symptoms,—while amblyopia and some other symptoms are often due to nodules in the nerves themselves.

The long retention of the axis cylinders accounts for the usual presence of paresis rather than paralysis, for the anæsthesia being slight, for the amblyopia rarely advancing to complete blindness, etc. (In locomotor ataxia there are also numerous axis cylinders in the sclerosed area, and the symptoms usually point to only a partial loss of function.) Charcot attributes the tremor to the same condition. He supposes that the axis cylinders continue to carry voluntary impulses, but, because they are bared of their medullary sheaths, they carry them in an irregular, jerking manner, and hence the oscillations in the voluntary movements. While this must be considered a mere theory, we can speak with more positiveness of the location of the lesion as a cause of the tremor. It seems to be due to nodules in the medulla and pons, or, at least, in the basilar portions of the brain. In a few cases, in which the disease was limited to the cord, no tremor was observed. On the other hand, when tremor was observed during life nodules were always found in the medulla and pons; when it was not observed, these parts were not affected to any extent.

With a considerable degree of doubt, we may attribute the nystagmus to lesions in the corpora quadrigemina, the scanning speech to lesions in the medulla, the vertigo to lesions in the medulla or cerebellum. A satisfactory explanation of the apoplectiform attacks has not yet been given.

DIAGNOSIS.—In some instances a diagnosis is made with the greatest ease, in others it is almost impossible to make a diagnosis. The most common clinical picture—paresis of the extremities with exaggerated tendon reflexes, intention tremor, nystagmus, scanning speech, amblyopia, etc.—is so characteristic that it cannot be mistaken.* But some of the most characteristic symptoms may be wanting, and then the diagnosis is much more difficult. In this case the indications of multiplicity of lesions and the very chronic course of the malady must be the guides to diagnosis. When the disease is limited to the spinal cord one can scarcely do more than guess in distinguishing it from other forms of myelitis. In such cases one must be on the lookout for cerebral symptoms. Optic atrophy is often a valuable diagnostic symptom, not only in this instance, but in excluding hysteria or other functional diseases which may simulate multiple sclerosis.

When the sclerosis affects only the brain it may present some of the manifestations of brain tumor. Here, too, the indications of a multiple lesion and the very slow course of the disease may clear up the diagnosis. But there is another important distinction, in that brain tumors produce to a large extent general symptoms, those of intracranial pressure, such as severe headache, convulsions, and double optic neuritis; while sclerosis produces merely local symptoms, those indicating the loss of function of the part affected by the disease.

The tremor of alcohol, lead, and mercurial poisoning might be mistaken for this disease, but concomitant symptoms and the history of a cause will establish the diagnosis. The tremor of paralysis agitans, with which this disease was formerly confounded, is easily distinguished by the appearance of the tremor, its being controlled to some extent by voluntary effort and increased during rest, and its very rarely affecting the muscles of the head and neck. Furthermore, paralysis agitans is

rarely found in persons under forty years of age, while multiple sclerosis rarely occurs after thirty, and, apart from the tremor, the symptoms of the two diseases are quite different.

PROGNOSIS.—Charcot believes that the disease may sometimes be cured, but the opposite view is generally entertained, though its arrest and even improvement for a number of years have been observed. It usually runs a very protracted course. When at its inception it manifests itself in various parts of the nervous system at the same time, it is likely to run a more rapid course. The occurrence of apoplectiform seizures, cystitis, bulbar symptoms, etc., indicates the approach of a fatal termination.

TREATMENT.—The same treatment is applicable as in other forms of chronic myelitis. (See *Spinal-Cord Diseases* in Vol. VII.)

Philip Zenner.

NERVI.—The town of Nervi stands upon a narrow, shelf-like plateau which intervenes between the base of an outlying spur or side range of the Apennines and the shore of the Mediterranean Sea, at a point some six miles distant from Genoa, in a southeasterly direction. The general trend of the coast line along what is known as the Riviera di Levante, or Eastern Riviera, between Genoa and Spezia, is from northwest to southeast; but, as in the case of the Western Riviera, the regularity of the line is frequently interrupted by the occurrence of bays, which are guarded by rocky headlands, jutting into the sea from the main chain of the Apennines, just as similar headlands along the Western Riviera reach down to the sea from the Maritime Alps. The scenery along this coast is consequently very similar to that of the Western Riviera, and, as the writer can testify from personal experience, it is exceedingly picturesque and beautiful. The width of the little plateau upon which Nervi is built does not exceed a quarter of a mile; its elevation above sea-level is very inconsiderable, and probably does not exceed one hundred feet. The shore line at Nervi runs nearly due east and west; the spur or side chain of the Apennines already mentioned, consisting of three separate mountain peaks, extends parallel with the shore, immediately back of the town. The most westerly and terminal peak of this side range is only about seven hundred or eight hundred feet high, and it is covered to its top with a growth of olive trees; the other two peaks are much higher (about twenty-five hundred feet), and their summits consist of bare rock.

The town of Nervi has a population of a little over three thousand, and it is built, in the straggling fashion so familiar to travellers who have visited the Italian coasts, along the old Genoa and Spezia post road. At this point the road does not skirt the shore, but hugs the base of the hills, so that the town stands close under the shelter of their steep slope, and is effectually protected from northerly winds. From easterly winds it is, in common with all points along the Eastern Riviera, protected in great measure by the main chain of the Apennines. The northeast wind is not effectually kept out, but gains access through gaps in the hills, and is sometimes strongly felt at Nervi. "The northwest wind," says Dr. Sparks, "is also not unknown, and Dr. Thilenius says of it, 'The most dangerous wind and the wind which is always the most violent, is the cold, cutting, dry, and bitter northwest.'" The warm, damp, relaxing "scirocco" wind, blowing from the southeast, is also of frequent occurrence.

The rainfall at Nervi is heavier than along the Western Riviera. The average fall in each of the six colder months of the year, derived from seven years of observation, is quoted by Dr. Sparks from Dr. Thilenius as follows: November, 6 inches; December, 4.88 inches; January, 4.78 inches; February, 3.23 inches; March, 4.49 inches; April, 2.20 inches. In the winter of 1876-77 the number of rainy days, including days on which slight showers occurred, during the months of December, January, February, and March, was 48. At Mentone, during the same period, 27 such days occurred (Sparks). This

* Schuler reported a case of tumor of the right hemisphere, in the neighborhood of the island of Reil, which produced the typical clinical picture of multiple sclerosis, and Westphal reported two cases with similar histories, in which no pathological changes were found post mortem. But these are such rare occurrences as not materially to impair the diagnostic value of this clinical picture.

season is spoken of by Dr. Sparks as a comparatively dry one. The winter of 1874-75, on the other hand, appears to have been at Nervi an exceptionally wet one, for Dr. Sparks quotes Dr. Thilenius to the effect that during that season "it rained almost incessantly for three months, day and night, and the air was so saturated with moisture that there was scarcely any difference between the wet- and dry-bulb thermometers." In the comparatively dry seasons of 1875-76 and 1876-77 the mean relative humidity, measured by August's psychrometer, and quoted by Dr. Sparks from Dr. H. J. Thomas, of Baden-Weiler, was as follows:

	Dec.	Jan.	Feb.	March.	April.
1875-76	64.0	60.0	64.8	66.7	72.7
1876-77	75.0	63.2	61.4	68.5

Dr. Kisch³ gives the mean relative humidity of Nervi as 62.9 to 66.6 per cent. So far as these figures go, they appear to indicate greater dryness of the atmosphere at Nervi than exists at Mentone, yet Drs. Weber² and Sparks¹ both pronounce the climate of Nervi to be moist-er than that of Mentone.

At Genoa, which, it will be remembered, is only six miles distant, the mean relative humidity is decidedly less than it is at Mentone, and during the prevalence of northerly winds it falls very low indeed, below twenty per cent.; occasionally as low as eight or nine per cent. On the other hand, when the "scirocco" blows, the air at Genoa becomes very moist. Dr. Hann, in his "Hand-buch der Klimatologie," gives the mean relative humidity of Genoa, for the five months November to March, as fifty-seven per cent. Now the free exposure of Nervi to the moisture-laden southerly winds and its shelter against the cold, drying, northerly winds characteristic of the Genoa climate, would no doubt combine to effect a great modification of the mean of humidity at the former place when compared with that of the latter; a modification, namely, in the direction of a higher percentage of saturation. Yet, taking into account the close proximity of Nervi to Genoa, and the relative humidity figures for Nervi given in Dr. Sparks' book, it seems not impos-sible that this writer and Dr. Weber, in pronouncing the Nervi winter climate moister than that of Mentone, have confounded the two factors of rainfall and humidity. The rainfall of Genoa is far greater than it is along the Western Riviera; the mean relative humidity is, on the other hand, very considerably less; and no better exam-ple than this feature of the Genoa climate can be adduced in support of what has already been said in the article on *Climate* (first edition), viz., that "The humidity of the at-mosphere can by no means be measured by the amount of the rainfall." Probably the variations in the atmospheric humidity at Nervi are much greater in amount and more frequent in occurrence than they are at Mentone. "In spite of its raininess," says Dr. Sparks, "the soil of Nervi —clay slate—is favorable to its rapid drying."

As to the winter temperature of Nervi, it appears to be about the same as that of Mentone. Dr. Kisch³ tells us that the temperature of the two places is similar in re-spect to its mean and to its variations. The observations of General Brocchi, during the years 1849-64, give the mean temperatures of November and December for thir-teen years, and those of January, February, March, and April for fourteen years; they are quoted by Dr. Sparks¹ as follows: November, 55.31°; December, 47.84°; Jan-uary, 46.36°; February, 47.8°; March, 49°; April, 58.1°.

The absolute reliability of these figures is not vouch-ed for by Dr. Sparks, as he explains that he "knows noth-ing of the arrangement of the instruments or hours of reading."

The following table, showing a comparison of the Nervi and Mentone temperatures for a single winter, is quoted from Dr. Sparks' book, its figures being derived from calculations by Dr. Sparks, based upon observations published by Herr Schulze, in his work on the health re-sorts of the Riviera, and of Middle and Lower Italy.⁴

TEMPERATURES AT NERVI AND AT MENTONE, WINTER OF 1874-75. (Sparks.)

	Nov.	Dec.	Jan.	Feb.	March.
Mean temperature at 8 A.M.					
Nervi	58.0	52.0	51.0	44.0	49.0
Mentone	54.0	48.2	50.5	44.5	49.8
Mean temperature at 2 P.M.					
Nervi	59.5	56.5	58.0	50.3	55.4
Mentone	59.2	53.6	56.0	59.0	57.5
Maximum temperature.					
Nervi	70.5	56.0	66.0	61.0	64.0
Mentone	70.5	64.0	64.0	55.0	66.0
Minimum temperature.					
Nervi	44.0	41.0	44.0	36.0	44.0
Mentone	46.0	42.0	46.0	36.0	48.0

The following data for mean temperature at 8 P.M. and for absolute minimum temperature at Nervi, during the months of December, 1876, and January, February, and March, 1877, are quoted by Dr. Sparks from an article by Dr. H. J. Thomas in the *Berliner klinische Wochenschrift*. The figures for the mean temperature are as follows: December, 51.5°; January, 49.3°; February, 47.2°; March, 47.4° F. The minimum temperature observed was 35.2° on March 2d, 1877. It is worthy of note, in connection with this last-quoted figure, that a minimum temperature of 25.5° was recorded in the "West Ray" of Mentone during this same month. Moreover, if one may judge from a table of monthly highest and lowest tem-peratures at Mentone which is given by Dr. Sparks in his account of that place, it would appear that this winter season of 1876-77 was not an unusually warm one on the Western Riviera, and that March, 1877, was exceptionally cold; and it is reasonable to infer that such was also the case along the Eastern Riviera. If such was the case, and if Dr. Thomas' observations were made under like con-ditions with those of Messrs. Freeman and Andrews at Mentone, the greater mildness, or, at least, the greater equality of the Nervi as compared with the Mentone climate would be illustrated, although not accurately measured, by these two figures alone.

On the other hand, Dr. Thomas' 8 P.M. figures, when compared with the daily mean figures of Dr. Brocchi, already quoted, show a decided discrepancy between the two sets of observations, especially if we assume, on the authority of the Mentone figures, that at Nervi the win-ter of 1876-77 was no warmer than the average.

It is to be regretted that no fuller, more extended, and more accurate observations respecting the various climatic factors of the place have as yet been made and recorded at Nervi. Nevertheless, so far as temperature is con-cerned, the climate is undoubtedly a mild one, and almost identical in this respect with that of the Western Riviera. As remarked by Dr. Sparks: "In spite of the want of really scientific observations on the climate of Nervi, there is no doubt of the mildness of its climate. The abundant subtropical vegetation, and the growth of standard lemon trees, is a proof of this." The following quotation from an article by Dr. Edward Houghton (Lon-don *Lancet*, December 13th, 1884) is interesting as illus-trating the agency of mountain shelter in the production of Nervi's mild winter temperature. In February, 1884, this gentleman visited Genoa, Pegli, and Nervi, all on the same day, for the express purpose of making ob-servations on this point. "The result," as he tells us, "was that the wind, which was bitterly cold at Genoa, was much milder at Pegli, especially in the valley behind the town, while it was perfectly calm, and even warm at Nervi, so long as the headlands which protect the place were not rounded by the visitor." The same point is further exemplified in a striking manner, although on a small scale, in what Dr. Sparks tells us concerning a sheltered coast-walk at Nervi itself; and everywhere along this part of the Italian coast we find that shelter from cold wind and exposure to the sun combine in vary-ing degrees to cause marked elevation of temperature, even "in the dead of winter." At Nervi the railway runs between the town and the sea. "Below the rail-

way, and just before the rocky shore takes its deep descent into the sea, a path a few feet wide has been cut along the edge of the rock for the use of the coast guardsmen, and as it accurately follows the indentations of the coast line, and is absolutely protected from the north by high garden walls, or by part of the rocky slope, or the railway embankment, while it gets all the southern sun in its full force, it is naturally an excellent promenade for invalids. Here they can walk or sit, or, if they choose, at certain points descend close to the sea, and enjoy a temperature of 64°–68° F., while in the High Street of Nervi the thermometer at the same time is not higher than 43° or 44°. Naturally great care is necessary to be provided with plenty of wraps to put on when returning from the shore to the town."

Of amusements for the invalid there appears to be a great dearth at Nervi, and the facilities for the making of excursions in the immediate neighborhood are exceedingly limited. "The neighborhood of Nervi," says Dr. Sparks, "offers but a limited field for excursions owing to the nearness and steepness of the high hills at the back of the town. There is no drive along the shore close to Nervi, though further west the road at some places nearly overhangs the sea. . . . For amusements of all kinds, except rod-fishing, Nervi presents little opportunity."

[There are three first-class hotels at Nervi and various pensions. A train runs every quarter of an hour to and from Genoa. "The mild but tonic climate of Nervi has for some years been attracting every season an increasing number of visitors." English physicians are to be found at Nervi.—E. O. O.]

Concerning the class of invalids who should be recommended or permitted to pass a winter at Nervi, it is impossible to decide with any degree of precision until a longer and more thorough series of meteorological observations shall have given us a more accurate knowledge of the local climatic peculiarities. For the present it can only be said that the general features of the climate are those of the Italian Riviera, and that the local modifications are such as render the climate less exciting than that of the Western Riviera resorts. *Huntington Richards*.

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- 4 Die klimatischen Curorte der Riviera, Mittel- und Unter-Italiens.
- 5 The Riviera, by C. B. Black, 1901.

NEURENTERIC CANALS.—It is now known that during the very early stages of the development of many vertebrates there is an open communication between the posterior portion of the medullary canal (spinal cord) and the entodermic or intestinal canal. To this communication the name of neurenteric canal has been applied. The original opening of the archenteron is known as the blastopore (see Vol. II., p. 4). In mammals, as in other amniota, it is represented by the posterior opening to the exterior of the notochordal canal. It has now been observed in various vertebrates that as the neural ridges or medullary plates develop backward they terminate against the sides of the blastopore, which acquires an elongated form. By their further growth the medullary plates close over across the long blastopore, in such a manner as to divide it into an anterior portion and a posterior portion. The posterior portion remains permanently open in certain amphibia and thus gives rise to the anus, or it may close over (Fig. 5159, *bl.*, and subsequently open, thus giving rise indirectly to the anus. The anterior portion is an opening enclosed within the medullary plate or groove, and may remain open until after the groove has closed to form a canal (Figs. 5159, 5160, *ne*), the true neurenteric canal, which establishes a direct communication between the neural and entodermal tubes. It has been observed in man (Fig. 5161, *New. c*). It might with propriety be termed the canal of Kowalewsky, from its discoverer. Kowalew-

sky first found it in amphioxus, and subsequently demonstrated its occurrence in various fish types.

The canal lies in front of the true or secondary blastopore and traverses the notochord. According to Dur-

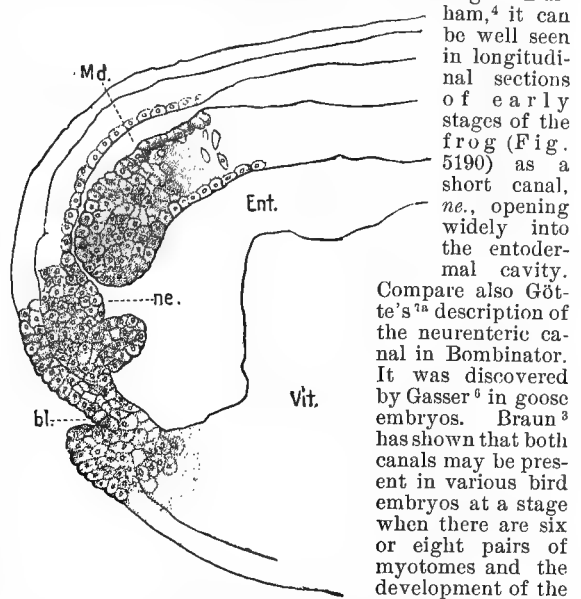


Fig. 5190.—Longitudinal Section of a Frog's Ovum shortly after the Closure of the Medullary Groove. The blastoporic canal, *bl.*, is only partially cut, but was found open in neighboring sections. (After Durham.) *Md.*, Medullary canal; *bl.*, blastopore; *Vit.*, yolk forming the floor of the entodermic cavity, *Ent.*; *ne.*, neurenteric canal.

ham,⁴ it can be well seen in longitudinal sections of early stages of the frog (Fig. 5190) as a short canal, *ne.*, opening widely into the entodermal cavity.

Compare also Götte's^{1a} description of the neurenteric canal in Bombinator. It was discovered by Gasser⁶ in goose embryos. Braun³ has shown that both canals may be present in various bird embryos at a stage when there are six or eight pairs of myotomes and the development of the tail is just beginning. The neurenteric canal lies a short distance in front of the blastopore, which is the larger of the two. The two canals appear in some species

at the same time, or in other species at slightly different stages. The posterior canal is more often obliterated in birds than the anterior. In the duck and in *Motacilla flava* the canals are separated both in the times and positions of their occurrence; in the Australian paroquet they are both present contemporaneously, although the neurenteric passage becomes open earliest. Fig. 5191 represents a transverse section, which passes through the neurenteric canal of the paroquet. In the common fowl the blastoporic canal appears not

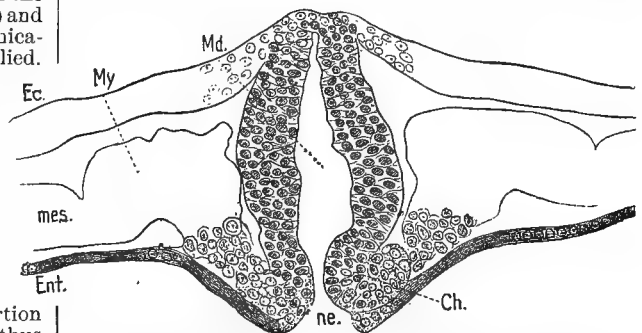


Fig. 5191.—Transverse Section of an Embryo Paroquet (*Melopsittacus*) to show the Anterior or True Neurenteric Canal. *Ec.*, Ectoderm; *My.*, myotome; *Md.*, medullary canal; *Ch.*, notochord pierced by the short neurenteric canal, *ne.*; *Ent.*, entoderm; *mes.*, mesoderm. (After Max Braun.)

to be open at any period after the formation of the primitive streak.

Another canal, which was first satisfactorily described by Braun,³ occurs in older embryos. The "Enddarm" of Gasser and Kölliker becomes the "Schwanzdarm"

(post-anal gut, Balfour¹) of older embryos, which soon becomes divided, at least in birds, into a dilated terminal portion and a narrower neck communicating with the intestine proper. The posterior section then subdivides, and its narrow end segment lengthens out and unites with the spinal cord. This canal we may designate as Braun's canal. It is not improbable that it is homologous with the amnio-allantoic canal of Gasser,⁷ which Rauber¹² has nicknamed the Cochinchina canal, after the breed of hens in which it seems most constant. In the one case we may suppose the canal to open after,

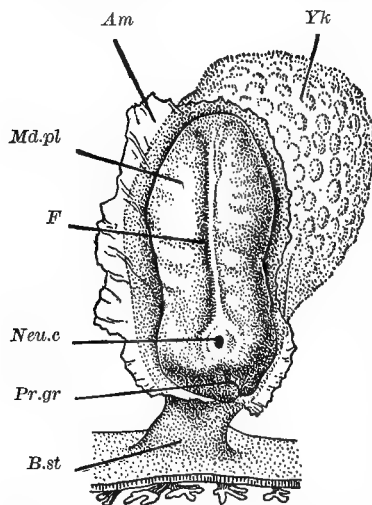


FIG. 5192.—Reconstruction of a Human Embryo 1.54 mm. Long. The amnion has been opened to show the dorsal surface of the embryo. Yk, Yolk sac; Am, amnion; Md.pl, medullary plate; F, dorsal furrow; Neu.c, neurenteric canal; Pr.gr, primitive groove; B.st, body stalk. (After Count Spee.) (From Minot's "Embryology," Blakiston, Phila., 1903.)

further said that the canal is identical with Kupffer's myelo-allantoic canal; it cannot be brought into relation with the development of the allantois, as believed by Kupffer,¹⁰ as the allantois and Enddarm are both formed before the canal appears.

The significance of the three canals is obscure. The middle one seems unquestionably the temporarily open secondary blastopore. The first, or Gasserian canal, is distinct from the blastopore, as the two coexist, and it seems desirable that this canal alone should be called *neurenteric*. As to its origin or significance nothing definite can be said, but it may be suggested that it was the excretory opening of the central canal of the spinal cord and that the cilia of the canal served to expel the fluid (compare Balfour^{1,2}). This may have been the condition in the earliest vertebrates, and the neurenteric canal now persists as a rudimentary organ. As to the morphological or physiological interpretation of the third or Braun's canal no satisfactory suggestion has been made.

It seems not impossible that a persistent neurenteric canal may occur as an excessively rare anomaly in the adult.

Charles Sedgwick Minot.

LITERATURE.

The literature of the neurenteric canals is all comparatively recent, and is, for the most part, included in essays dealing with other embryological subjects. Great confusion has arisen from the failure to distinguish the several canals. The reader will find his way most readily by consulting first the text-books of Balfour,^{2,6}; secondly, the article of Braun,⁸; and third, Rauber's note,¹² although Rauber's terminology is eccentric and perplexing.

¹ Balfour, F. M.: On the Early Development of the Lacertilia, etc. Quart. Journ. Microsc. Sci., xix. (1879); also in his Works, i., p. 644, with Plate 29.

² Balfour: Comparative Embryology, vol. ii., pp. 267-269.

³ Braun, M.: Die Entwicklung des Wellenpapageis; II. Theil, Semper's Arbeiten, v., 205-341, Taf. x.-xiv. (a valuable but excessively diffuse article. The most important passages on the neurenteric canals are on pp. 296, 301, and 308).

⁴ Durham, Herbert E.: Note on the Presence of a Neurenteric Canal in Rana. Quart. Journ. Microsc. Science, xxvi., 509-510, Plate xxvii.

⁵ Foster and Balfour: Elements of Embryology, second edition, 1883.

⁶ Gasser: Der Primitivstreifen bei Vogel-Embryonen, Cassel, 1879.

⁷ Gasser: Beiträge zur Kenntniss der Vogelkeiminscheibe. His und Braune's Archiv, 1882, 399-398.

⁸ Götze: Entwicklungsgeschichte der Unke.

⁹ Heape, Walter: The Early Development of the Mole (Talpa Europaea). The formation of the germinal layers, and early development of the medullary groove and notochord. Quart. Journ. Microsc. Sci., xxvi., 1883, 412-452, Plate xxviii.-xxxi.

¹⁰ Hoffmann, C. K.: Die Bildung des Mesoderms, die Anlage der Chorda dorsalis, u. die Entwicklung des Canalis neurentericus bei Vogel-Embryonen, p. 109, 5 Tafeln. Amsterdam, 1883. (Abstr. in Hoffmann u. Schwalbe's Jahresber., 1883, 442-444.)

¹¹ Kupffer, C.: Die Gastrulation an den meroblastischen Eiern der Wirbelthiere und die Bedeutung des Primitivstreifs. Arch. Anat. u. Physiol., Anat. Abth., 1882, 1-30, Taf. i.-iv. Fortsetzung, 139-156, Taf. viii.-ix.; 2te Fortsetzung, 1883, 1-40, Taf. i.-ii.

¹² Lieberkühn, N.: Ueber die Chorda bei Säugethieren. His und Braune's Archiv, 1882, 399-433, Taf. xx.-xxi. Fortsetzung, 1883, 435-452, Taf. xix.

¹³ Rauber, A.: Noch ein Blastoporus. Zool. Anzeiger, vi., 1883, 143-147, and 163-167 (cf. his earlier papers on the Blastopore Canal, Zool. Anzeiger, ii., 1897, p. 499, and iii., 1898, p. 180).

¹⁴ Strahl: Ueber Canalis neurentericus und Allantois bei Lacerta viridis. His u. Braune's Arch., 1883, 323-340, Taf. xiv.

NOVASPIRIN is methylene-citryl-salicylic acid. It is a white, odorless, crystalline powder with an acid taste; easily soluble in alcohol, slightly so in chloroform and ether, not perceptibly so in water. It is said to contain sixty-two per cent. of salicylic acid, is decomposed upon heating with caustic alkalies or standing in water or alkaline solutions. Novaspirin is another one of the many salicylic-acid derivatives or combinations and is used in the same doses, 0.7 to 1.0 gm. (10 to 15 grains), and for the same purposes as the salicylates.

John W. Wainwright.

NOVOCAIN is another of the many local anæsthetics recently offered as substitutes for cocaine. It is chemically the p-amino-benzoyl-diethyl-amino-ethanol hydrochloride, $\text{NH}_2\text{C}_6\text{H}_4\text{COO.C}_2\text{H}_4\text{N}(\text{C}_2\text{H}_5)_2\text{HCl}$. It occurs as colorless needle-like crystals which melt at 156° C. It is soluble in equal parts of cold water and 1 part to 30 parts of alcohol. Solutions are neutral, are incompatible with caustic alkalies and their carbonates; sodium bicarbonate, however, does not cause turbidity of novocain solutions. Pharmacological studies show novocain in the same concentrations to have an equal action on the peripheral nerves as does cocaine, while the action is more prolonged. Irritation is not in evidence even in the strongest concentrations, while circulation and respiration are uninfluenced. Intravenous injections are followed by a brief lowering of the blood pressure, while the respiration becomes slower and shallower. The heart beats are not weakened. It therefore doubtless acts upon the vasomotor centres.

A comparison of the fatal dose on different kinds of animals with that of cocaine and stovain show per kilo of body weight by subcutaneous injection as follows:

Cocaine.	Stovain.	Novocain.
Rabbits...0.05 to 0.1 gm.	0.15 to 0.17 gm.	0.35 to 0.4 gm.
Dogs....0.05 to 0.07 "	0.15	0.25

The same ratio follows when it is applied intravenously. Injected into the spinal cord the fatal doses for cats are:

Cocaine.	Stovain.	Novocain.
0.018 gram.	0.025 to 0.05 gram,	0.15 gram not fatal. (Biberfeld.)

From these results it therefore appears that novocain is from five to six times less toxic than cocaine and two to three times less than stovain.

In superficial infiltration, conduction, and lumbar anæsthesia, novocain, alypin, and stovain all seem to be superior to cocaine, and as no cases of habit have been reported from their use it would seem that they should find employment when possible. It is a fact, however, that cocaine will not be entirely displaced by these newer products, as for certain kinds of work it surpasses the latter. The strength of novocain solution is from $\frac{1}{2}$ to 2 per cent. when injected into the tissues; 10 per cent. in ophthalmology; 5 to 10 per cent. when applied to the mucous membrane. It should, as a rule, be used in connection with one of the suprarenal principles, smaller quantities of both being used when combined than when used singly. It can be sterilized by boiling, which should precede the addition of

TABLE GIVING PARTICULARS OF ALL THE REPORTED CASES OF OCHRONOSIS.

Case.	Author and reference.	Sex and age.	Color of skin.	Other parts colored.	Urine color and reactions.	Other diseases.	Length of illness.	Illustrations in report.	Microscopical details.
1	Virchow: Virchow's Archiv, 1866, Band xxxvii., p. 212.	M., 67.	No description, presumably unaltered.	All cartilages.	Clear; no account of reaction.	Aneurism, ascites, hydrothorax, and arthritis deformans.	?	Colored pictures of blackened cartilages (macroscopical).	Brown coloration of ground substance; granular pigmentation of cartilage cells.
2	Boström: Virchow's Festschrift, Band ii., 1891, p. 177.	F., 44.	No reference.	Cartilages ebony black; also spots on valves and endocardium of heart (brownish gray).	No reference.	Strangulated umbilical hernia.	?	None.	Pigment generally distributed in ground substance of cartilages; granular in cells.
3	Hansemann: Berliner klinische Wochenschrift, 1892, Band xxix., p. 660.	M., 41.	No alteration.	Cartilages of ribs, sternoclaviculars, intervertebrals, etc., inky black.	Black; no reduction of copper; no homogentisic acid. <i>Not alkaptonuria</i> (Langstein).	General oedema and aneurism of the left ventricle.	18 years.	None.	Details given in Langstein; Hofmeister's Beiträge, Band iv., p. 145, on Urine; also Zdarek: <i>ibid.</i> , p. 378.
4	Heile: Virchow's Archiv, 1900, Band clx., p. 148.	F., 36.	No alteration.	Cartilages of ribs jet black; cartilages of larynx and trachea only colored in periphery.	No notes.	Peritonitis and ruptured tubal pregnancy.	?	Microscopical appearances of cartilages and lymphatic glands.	Fine granular pigment in ground substance.
5	<i>Ibid.</i>	F., 62.	No alteration.	All cartilages.	No change.	Chronic ulcer of leg and mitral-valve disease.	Many years.	As above.	Same as above.
6	Hecker and Wolf: Festschrift des 50 Jahr. Best. d. Stadt Krankenhaus zu Dresden, 1899, p. 325.	M., 73.	A dun ash color, brownish in places.	Patch on sclerotics; all cartilages; dura mater in spots.	Brown, becoming black on standing; no sugar or albumin. <i>Not alkaptonuria</i> .	General arteriosclerosis, softening of cerebellum, myocarditis, stenosis and inefficiency of aortic valves, arthritis deformans, and osteomalacia.	Melanuria 11 years.	None.	General pigmentation of ground substance of cartilage; granular also in patches; granular in dura mater.
7	Albrecht: Zeitschrift für Heilkunde, 1902, Band xxiii., p. 366.	M., 47.	During life pale (<i>blass</i>). Post mortem, no marked pigmentation.	Rib cartilages; chordæ tendineæ of the heart.	Dark, reduces copper; all reactions of alkaptonuria except homogentisic acid? <i>Alkaptonuria</i> .	Pulmonary tubercle.	?	None.	Microscopy nil.
8	Osler: The Lancet, Jan. 2, 1904, p. 10.	M., 57, Living.	Coal-black on the nose and cheeks; patches on sclerotics; ears blue-black.	Spots on the back of the hands.	Clear when passed, becoming black on standing. <i>Alkaptonuria</i> .	Anæmia; weak, irregular heart; and Heberden's nodules.	More than 10 years.	None.	Still living (Jan., 1906).
9	<i>Ibid.</i>	M., 49, Brother of Case 8.	Normal; patches on sclerotics.	Ears showed blue-black through the skin; no post-mortem.	<i>Alkaptonuria</i> .	Died from pneumonia.	—	None.	None.
10	Ogden: Zeitschrift für physiologische Chemie, 1895.	? Living.	—	Pearly gray inside concha.	<i>Alkaptonuria</i> .	?	?	?	?
11	Pope: The Lancet, Jan. 6, 1906, p. 24.	F., 47.	Face brown; patches on sclerotics.	Rib cartilages blue-black; ears blue; inside of lips black patches.	Black. <i>Not alkaptonuria or true melanuria</i> .	Chronic ulcer of leg, phthisis, and sclerosis of adrenals.	Five years.	Superficial and microscopical appearances.	Fine granular pigment in cartilages; pigment in the white elastic tissue in the skin but not in rete Malpighii.
12	Pick: Case presented at Meeting of Berl. med. Society, Mar. 14, 1906. Dtsch. med. Wch. Vereinsbeil., No. 13, 1906, p. 524; Berl. klin. Woch., No. 17, 1906.	F., 77.	Bronze-skin complexion. Not brown throughout, but partly bluish. Hands and ears steel-blue. Brown spots in both palpebral fissures.	Pigmentation not limited to cartilages, but also found in heart-valves, vessels of lymph glands, etc. No special findings in other organs. Sole of the foot and toes free from pigmentation.	Urine free from albumin and sugar.	Chronic varicose veins of legs with ulceration. Thickening (mild elephantiasis) of feet. Chronic arthritic changes of fingers of both hands.	Discoloration of ears began 16 years ago. Change in face, eyes, and hands came on gradually in last 4 years.	—	Pigment not invariably diffuse, but also granular. Free from iron; soluble in alkali; related to melanins.

the suprarenal principle, as this is injured by boiling. It is wise, with this as with other similar products, to prepare the solution fresh when wanted, or at all events if a stock solution of any of the local anesthetics is kept on hand, the suprarenal preparation should not be added until ready for use, as all of these organic or gland products are more or less unstable and a chemical reaction is likely to take place if a solution of the two principles is kept on hand for any length of time.

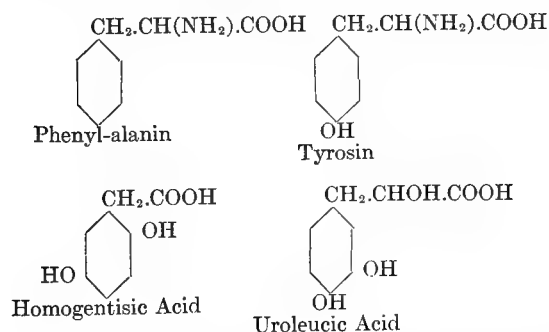
As in the case of alypin, a nitrate of novocain is to be had which can be used with silver nitrate to lessen the pain following the application of the latter to inflamed tissues, such as the urethra, bladder, etc. It may also be used alone or with a suprarenal principle to anesthetize the urethra before dilatation or the introduction of instruments.

The percentage solution recommended is the same as of the novocain. $\frac{1}{2}$ to 2 per cent.

John W. Wainwright.

OCHRONOSIS.—This is a rare condition in which the cartilages (and sometimes other tissues, such as the loose connective tissues, smooth and striated muscle fibres, and epithelial cells) are found to have undergone a pathological pigmentation; in other words, it is a form of melanotic pigmentation. This pigmentation is supposed to be produced by a substance similar to, and very closely related to, melanin; and is said to be due to the action of the enzyme tyrosinase on tyrosin and phenyl-alanin. Ochronosis has also been observed after a prolonged administration of phenol, as well as in connection with disorders of the suprarenals. The ochronotic pigmentation may affect external parts, such as the hands, ears, sclera, skin of the face with inner surface of the lips, to a marked extent. These pigmentations constitute a clinical sign of ochronosis, so that the disease may be diagnosed during the life of the patient. The pigment may be excreted by the urine, which then becomes dark on being exposed to the air; in these cases pigmented casts may also be found in the urine. Such casts are considered by Pick as pathognomonic of ochronosis.

The question of the relation of ochronosis to alkaptonuria has been debated; but the two conditions are not necessarily associated, and either can occur without the other; Garrod thinks that alkaptonuria may be a cause, but not the only cause, of ochronosis. Still, the possibility of a relation between these two conditions (even if not a causal relation) must be allowed, particularly when we notice the constitution of uroleucic acid and homogentisic acid (to which alkaptonuria is due), and compare the same with the constitution of tyrosin and phenyl-anilin, which are supposed to be the causative factors of ochronosis.



Nardi has studied the occurrence of beginning ochronosis in the cartilages, especially those of the knee, in normal adult individuals up to eighty-five years of age. Every one of these cases came to autopsy from other causes; and pigmentation was positively demonstrated in fifteen out of fifty cases.

Upon the basis of his investigations, Nardi (*Archivio di Biologia*, Florence, lix., 1905, 496) arrives at the following conclusions: (1) The articular cartilages of adults frequently present pigmentations, which are as a rule of hæmatogenous origin. (2) The ochronotic pigment, besides being found in the cartilages, was also in the intima of the arteries, where it existed in large amount and in diffuse form, because the conditions and circumstances favoring its deposit had been present for a long time. (3) The fatty degeneration of the cartilage cells cannot be regarded as a change which specially favors the deposit of the ochronotic pigment, although in a general way the fats are known to have a marked affinity for the pigments. (4) It is possible, by means of repeated injections of homogeneous blood into the joints of animals such as rabbits, to produce in the cartilages a pigment possessing all the properties of the ochronotic pigment.

A complete résumé of the cases and literature up to the present time will be found in a table published in *The Lancet* of January 6th, 1906.

R. J. E. Scott.

OPHTHALMO-REACTION IN TUBERCULOSIS AND TYPHOID FEVER.

—The physical examination for tuberculosis, particularly in the earlier stages or incipient form, is attended with many disappointments, in fact in the hands of the average general practitioner has been a failure. Since the determination of the tubercle bacillus the microscope has been of inestimable value, but even this has not solved the problem of an early diagnosis of tuberculosis, for the bacilli do not make their appearance, are not clearly in evidence in the sputum, at as early a stage of the disease as will give the greatest promise to begin treatment. Robert Koch's studies helped to solve the problem of an early diagnosis through the reaction following the subcutaneous injection of tuberculin, a reaction following in the majority of cases when tuberculosis exists; but here we encounter a wide-spread fear among the profession of inoculating the disease when it does not exist, or of lighting up latent tuberculosis; moreover, the technique for the application of this potent agent is so difficult as to discourage the average physician. Any innovation, therefore, which will promise as reliable results without the necessity for laboratory experience, must of necessity claim the attention of the profession. Such, indeed, is the ophthalmo-reaction test as used by Calmette of France, which consists in the instillation of a small quantity of a weak tuberculin solution into the eye, which will be followed by hyperæmia of the conjunctiva if the individual is infected. No reaction follows should the suspect be non-tuberculous. No constitutional symptoms result from this method, nor has serious injury to the eye been noted.

The conjunctiva is notably responsive to irritation and highly vascular. A comparison of the sclera of the two eyes will easily show the slightest degree of hyperæmia. Calmette's procedure is to precipitate the old or crude tuberculin with ninety-five-per-cent. alcohol, the precipitate being dried. The resulting product is entirely free from bouillon as well as from other by-products and glycerin. One per cent. of this substance is dissolved in filtered sterile physiological salt solution, and one drop of the resultant solution is instilled into one eye, under the lower lid, from an eye dropper. Care should be taken not to use more than one drop, or to allow any to come in contact with the cheek. The reaction is plainly marked if the subject is tuberculous in from three to eight hours by varying degrees of hyperæmia, lacrymation, and a feeling as of sand in the eye.

In from three to five hours after the instillation those having tuberculosis react as above. There is evident congestion of the palpebral conjunctiva which assumes a bright red color with more or less œdema. The lacrymal caruncle becomes swollen, red, and covered with a fibrinous exudate. The congestion gradually deepens and is accompanied by lacrymation. At the end of six

hours the fibrinous secretion becomes more profuse, gathering in filaments in the inferior conjunctival cul-de-sac. The reaction reaches its height in from six to ten hours. There is no pain, but a slight burning sensation with some interference with vision, this being proportionate to the amount of exudate. There is no chemosis and the temperature is not affected. The symptoms of congestion gradually subside and finally disappear at the end of eighteen hours in children, and of twenty-four to thirty-six hours in adults.

If the patient is non-tuberculous, the redness of the conjunctiva is mild, appears in from one and one-half to three hours, and promptly subsides without the fibrinous secretion or lacrymation. Calmette's results have been confirmed in more than one thousand cases and by numerous observers.

Contraindications for the use of this test are all diseases of the conjunctiva, eyelids, or cornea, including hay fever, ulcers, trachoma, etc. The patient is best kept protected from a strong light during the test.

A second instillation may be made in the other eye after forty-eight hours, should there be no reaction following the first.

Baldwin of Saranac Lake, New York, uses a 0.5 percent. solution in the first application and 1-per-cent. if a second is made. The application is made at all ages, but has been used by Baldwin in most of the reported cases in children. Autopsies have in a number of cases confirmed the findings.

Baldwin reports 137 cases. He found 42 positive reactions out of 45 tuberculous subjects tested, 1 doubtful, 2 negative. In 9 cases of healed pulmonary or other tuberculous lesions, 8 reacted, 1 negative. In 26 cases of suspected tuberculosis, 3 reacted, 4 were doubtful, and 14 negative. In 57 apparently healthy individuals in whom the test was made 16 gave a positive reaction, 1 was doubtful, and 40 were negative.

(See also the article on *Cuti-reaction*.)

The ophthalmic-reaction has also been employed by Chantemesse as a diagnostic measure in typhoid fever. He has prepared a typhoid-fever toxin, $\frac{1}{10}$ mg. of which, when dissolved in a drop of sterile water and instilled into the eye of a healthy person, caused reddening of the conjunctiva with increased secretion of tears at the end of from two to three hours. These symptoms subsided after from four to six hours, and by the following day had disappeared entirely.

In typhoid-fever patients the reaction is much more violent, leading in some instances to a serofibrinous exudate. It reaches the maximum of intensity in from six to twelve hours and thereafter subsides very slowly, so that irritation phenomena can still be determined at the end of twenty-four hours, or in some instances of two or three days after the application.

This reaction was studied in rabbits which had been infected with typhoid bacilli. The procedure is regarded as reliable and harmless. The toxin employed is a dry powder obtained by precipitating with absolute alcohol a strong solution of soluble typhoid toxin.

John W. Wainwright.

OPSONIC THERAPY.—(Synonyms: Opsonotherapy; Opsonic bacterial therapy; Vaccine therapy; Bacterial vaccine therapy; Therapeutic bacterial inoculation; Therapeutic immunization.)

DEFINITION.—A method of biological therapy having as its essential practice the artificial inoculation of the causative microbe, and as its principle the theory of opsonins.

HISTORICAL.—Underlying the practice of opsonic therapy is the idea long held and frequently expressed in former times by thoughtful physicians, that in the disease is the element of its own cure. Nature provides man with defensive agencies which frequently operate spontaneously to combat disease successfully; this was the basic idea in medical philosophy long before the modern microparasitological era, and upon it various systems of therapeutics were founded. With the dis-

covery of the rôle that bacteria play in the causation of disease a great advance was scored, and the most brilliant of pioneers in this new field of biological inquiry the immortal Pasteur, immediately engaged himself with the task of applying the knowledge of pathogenic bacteria to the treatment of infectious diseases. It was this savant who disclosed the fact that a protective immunity could be secured by inoculating the susceptible organism with certain pathogenic bacteria whose activity had been modified by various agencies. One practical outgrowth was Pasteur's protective "vaccination" for anthrax; another, the well-known method of prophylactic vaccination against hydrophobia. The bacterial substances, or, as in the case of hydrophobia the infected tissue itself, were called "vaccines." Pasteur, and modifications of his method have been applied in protective vaccination against bovine pleuropneumonia, chicken cholera, rinderpest, Asiatic cholera, plague, and typhoid fever. Early among the attempts to effect therapeutic, as distinguished from protective results, by the introduction of bacterial substances were those of Robert Koch, whose tuberculin treatment of human tuberculosis was a step in the right direction and only unsuccessful, as it now appears, through error in its detail.

At the same time that Pasteur and his followers demonstrated the possibilities of protective bacterial inoculation, Buchner and many after him brought to light the important part played by the blood serum in immunity, while Metchnikoff and his school made plain the important rôle of the protective body cells or phagocytes, in the defence of the animal organism against microparasites.

It was at this stage in the development of microparasitology that Sir Almroth P. Wright began the searches from which developed the now famous theory of opsonins and the practice of therapeutic bacterial inoculation. As pathologist of the Army Medical School Netley, Wright's first considerable problem was that of protective antityphoid inoculation, his earliest published report upon it bearing the date September 19 1896. Studying the effects of these antityphoid inoculations; finding that agglutinative and bactericidal phenomena could be induced in human blood serum by a subcutaneous injection of devitalized typhoid bacilli, earlier workers had shown; endeavoring to discover means of measuring the reactions produced by antityphoid inoculations, and of accurately standardizing the bacterial vaccine, Wright step by step pursued the investigations leading to the discovery of therapeutic bacterial inoculation; and later still, with Douglas, to the discovery of the opsonic action of the blood serum. March, 1902, Wright made public his first paper dealing with "the treatment of furunculosis, sycosis, and abscesses by the inoculation of a staphylococcus vaccine, and generally on the treatment of localized bacterial infections by therapeutic inoculations of the corresponding bacterial vaccines"; and after the interval of more than a year, in October, 1903, he and Douglas announced the discovery of that special class of protective substances—*opsonins*. From this period numerous reports of Wright and his immediate associates have been recorded in the medical literature of Great Britain, and during the last year especially, similar reports have appeared in the United States.

It is well to recall in passing that Wright's fundamental practice of therapeutic bacterial inoculation rests upon the work of numerous previous investigators, being, indeed, but the wider application of methods already in vogue; and further, that he successfully practised therapeutic bacterial inoculations before the opsonic action of the blood serum was discovered, the opsonic index perfected; as one may see in the first publication dealing with therapeutic inoculation in which a standard of bactericidal action is offered as a means of gauging the effect of bacterial vaccines. Being convinced of the value of bacterial inoculations, as satisfied by large experience of his ability to use the

substances safely, Wright rapidly extended their field of usefulness; at the same time modifying these vaccines as to dosage and time of inoculation in a manner to give a new and successful impetus to a mode of practice previously recognized, but not perfected as to most essential details.

THE THEORY OF OPSONINS.—Brought to its simplest terms, Wright's theory of opsonins holds that, among other protective substances, the blood serum contains one, opsonin (from *ὀψωνία*, I convert into palatable pabulum), that acts upon pathogenic bacteria in such a manner as to prepare them for destruction by the protective body cells or phagocytes, principal among which are the multinuclear leucocytes.

The contention of Wright and Douglas that opsonin is a distinct ingredient in blood serum, with properties to distinguish it from other such protective or immunizing products as bacteriocidins, bacteriolysins, aggrsins, and agglutinins, is now gradually admitted; as is their claim that opsonic action is directly effective through a union of the opsonin with the bacterium as a preliminary to phagocytosis, and that this effect is not a stimulating one as concerns the phagocytes, nor one that directly deprives the bacterium of its vitality.

Some comparatively simple experiments suffice to demonstrate the presence of opsonin in the blood. First, there is taken a portion of freshly shed human blood and an equal portion of a suspension in physiological salt solution of a certain pathogenic bacterial organism, say, specifically, *Staphylococcus aureus*. These portions are mixed and subjected to a fifteen-minute sojourn at incubator temperature. Stained smears of the mixture are examined microscopically after incubation, and the well-known phenomenon of phagocytosis is brought to light; that is to say, the polynuclear leucocytes will be found to have ingested the micro-organisms. It was at this point in the experiment that those who advocated the theory of phagocytosis *per se* were content to rest. But a modification of the experiment serves to demonstrate the ineffectiveness of the leucocytes alone. Fresh human blood is caught in a decalcifying physiological salt solution, and by a process whose detail is described below the blood cells, including the leucocytes, are washed free from plasma which, of course, incorporates the serum. Such "washed" leucocytes, when mixed with a suspension of staphylococcus and incubated, exhibit an indifference to the microbes quite as striking as the greedy deportment of their fellows in the first experiment. If phagocytosis takes place at all, it is extraordinarily limited in degree. Still, a third experiment serves to show that the well-marked phagocytosis in the original test is dependent on one factor in addition to the vitality of the leucocytes; that is, the action of something in the blood serum. For if to the mixture of washed leucocytes and staphylococcus suspension, serum of recently coagulated human blood be added, phagocytosis proceeds as in the first test with whole blood. Hereby we obtain a demonstration of the opsonic action of the blood serum, by which is meant its effect of preparing the microbe for phagocytosis, and hence the derivation of the word, opsonin. By what experiments it was shown that opsonins are special and distinctive ingredients of blood serum, and that they are concerned wherever active phagocytosis (whether of bacteria or blood cells) goes on, cannot here be discussed. Suffice it to repeat that the fact of opsonic action and the presence of opsonins is generally admitted.

Normal and Immune Opsonins.—With the discovery of opsonins came the efforts to establish their relationship to various pathogenic bacterial species. Were opsonins specific, that is to say, did they possess predilection for certain bacterial species, or were they universal in relation to all disease-producing microbes? It was discovered that opsonic and phagocytic action were particularly active with those bacterial species belonging to the pyogenic group; and at first it was believed that special and distinct opsonins for the various microbic groups resided in normal serum. More recently,

under the impulse of extensive investigations, this view has been abandoned, and instead it is held that the blood serum of a non-infected individual contains a *normal* or *common opsonin* which is effective alike against various bacteria, and which is distinguished by being *thermolabile*, that is, of losing its effect on heating the serum containing it for ten minutes at 60° C. When, however, infection with a certain microbe takes place spontaneously, or when the phenomenon of infection is artificially produced by inoculation of this microbe, even though killed by regulated heating, opsonin with a special affinity of that particular microbe makes its appearance in the blood serum. These are the *immune* or *specific opsonins*, and are further differentiated by being *thermostable* under the conditions above mentioned.

The Nature of Opsonins.—With the testimony of careful experiments indicating the presence of special ingredients or opsonins in the blood serum, and the fundamental rôle of such opsonins in the process of phagocytosis, one naturally inquires as to the more intimate nature of these important substances. Viewed from the standpoint of Ehrlich's side-chain theory, for instance, what place is to be assigned to the opsonins? What relation do they bear to antitoxins, agglutinins, precipitins, lysins, and other antibodies whose peculiarities have been investigated under the impetus of Ehrlich's hypothesis? Are they identical with, or different from, other known antibodies? And what is their structure as compared with more familiar substances? On this head the views of investigators are still in discord. By some it is held that, since opsonin is destroyed by heat, its structure is similar to that of complements and toxins. Again, it is maintained that the thermolabile opsonins of normal serum belong to the group of complements, while the thermostable opsonin of immune serum possesses the comparatively specific character of antibodies in general. And further, it is asserted that since even normal opsonins, after loss of their power through heating, may have it restored or reactivated by addition of dilute unheated serum, they have a structure similar to hæmolysins and bacteriolysins, and depend for their qualities on the combined action of a thermostable portion, or amboceptor, and a thermolabile portion, or complement.

Opsonins and Infection.—With the refinement of method perfected by Wright and Douglas it becomes possible to measure with considerable accuracy the opsonic power of a given blood serum; the method is one in which the opsonic value of two or more serums is compared, giving the "opsonic index," the details in the prosecution of which test are presently to be described. As studied by the opsonic index certain important facts in relation to bacterial infections have been disclosed, chief among which is that, in a localized infection with one of the several bacterial species of the pyogenic group, the opsonic index is below normal. Sometimes in generalized infection the opsonic index is low, again high. The bearing of this varying opsonic index, and of the fluctuations that may be artificially induced in a given infection, will be more fully considered under the head of autoinoculation. But this is the point at which to emphasize the crucial feature of all this new work, viz., that the opsonic index seems to furnish a trustworthy guide to the immunizing responses which the infected organism is making in its combat against microbic infection. Expressed otherwise, it is to say that the opsonic index gives to the physician a means of measuring the resistance of the patient suffering from an infection, and of determining whether nature, unaided by artificial agencies, is waging a successful or unsuccessful struggle against that infection.

Opsonins and Bacterial Inoculations.—Besides the specific reactions aroused in the opsonic power of the blood by infection with specific microbes, there is a method of reproducing a similar phenomenon by artificial inoculation of the micro-organisms. To the inoculating substance, consisting essentially of the devitalized bacteria in a fluid suspension, the name

"vaccine" has been given by Wright, though, as has been pointed out, the term is unfortunate because of its generally accepted usage in connection with the protective virus of smallpox, and it is much to be desired that a substitute less clumsy than "opsonogen," and more euphonic than "bacterin," be settled upon. At any rate, the subcutaneous injection of such vaccines is accompanied by a series of events which can be followed with the aid of the opsonic index. It can be shown, for instance, that these artificial inoculations arouse specific or immune opsonins corresponding to the bacterial species, and further, if not used in too small a dose, nor one abnormally excessive, are accompanied with a well-defined wave of immunizing response. Thus the immediate effect is the lowering of the opsonic index as compared with normal serum, and this period of low opsonic content, accompanied as it usually is by some adverse constitutional reactions like languor, headache, chilliness, and slight fever, has been appropriately styled a "negative phase." After an interval of hours or days, the wave of immunity mounts to and above the normal, constituting the "positive phase," reaching the highest point or "high tide" of immunity. After a further interval, varying with different bacteria and according to dosage and other circumstances, the index falls once more and reaches the normal.

Opsonins and Therapeutic Immunization.—Such facts as have already been discussed have an interest to the worker in pure science, but there is another aspect of the theory of opsonins that comes home to the practising physician with an immediate appeal. This concerns the vitally important discovery that the machinery of immunization in man can be set in motion by bacterial vaccines, not only experimentally as just described, but in the midst of an existing infection, and by this agency there can be aroused new impulses of a therapeutic tendency. Or, in other words, *curative immunity* may be artificially stimulated through therapeutic bacterial inoculations. Compared with the other and more controversial features of Wright's contributions, this one, of reviving and placing on a satisfactory basis the practice of therapeutic bacterial immunization, is his really great achievement.

Gauged by the opsonic index, therapeutic bacterial inoculations, in the event of a satisfactory response, show the same wave as has been mentioned in connection with experimental artificial injection of bacterial vaccine. There comes at the outset the fall of opsonic power, or negative phase, and with it more or less constitutional disturbance, and at times temporary aggravation of the localized infection if such is under treatment. Now follows the rising wave of the positive phase, with constitutional betterment and improvement in local lesions. Before the immunizing wave has again receded too far, a second inoculation is performed with another characteristic rebound; and so on until a sustained "high tide" is produced, or until recovery has been effected.

Correct dosage and proper spacing of bacterial inoculations are vitally essential to successful therapeutic immunization, and as a guide to this desired end the opsonic index is recommended by Wright and his immediate followers as indispensable. Very elaborate charts representing a frequent measurement of the opsonic index are presented, involving, as any one knows who has qualified himself in the technique of the opsonic index, an immense amount of labor. Indeed, many recent contributions to the literature of practical opsonic therapy abound in beautiful charts, and exhibit a dearth of interesting and important clinical details. Nevertheless it is a fact, well established by those who have chosen to pursue the practice of therapeutic immunization without the guide of the opsonic index, that eminently satisfactory results can be secured in many morbid affections of microbial origin by inoculations guided by symptomatic indications, or at intervals previously determined by Wright or others using the opsonic index.

THE HYPOTHESIS OF AUTO-INOCULATION.—An out-

growth of Wright's studies upon opsonins is the li indirectly shed upon the spontaneous efforts of the man organism to meet and combat bacterial infect and the recent communications by this investigator occupied by an elaboration of his theory of auto-inoculation. According to these views, nature protects animal organism, in event of an infection, by auto-inoculation; which is to say that, from the infective bacteria or their products are set free in such a man as to evoke an immunizing response, and the success failure of this spontaneous auto-inoculation is evident by the successful or unsuccessful issue of the disease. Take typhoid fever, for instance. A constant self-generated inoculation with the typhoid bacilli or their products is going forth, one of the earliest manifestations of which is the heightened agglutinative activity of the infected individual's blood serum; and full recovery is achieved only when these natural inoculations have aroused the immunizing machinery to a point sufficiently high, and long enough sustained to permit conquest of the invading microbe. Imperfect response is heralded by clinical fluctuations, and failure eventually in death of the typhoid-infected host. Contemplated from a similar attitude it becomes clear why traumatic and surgical infective diseases run their various course from slight localized transient reactions to rapidly fatal septicæmias, or the tedious, spreading, suppurative processes of chronic pus-microbe disease. It is explainable why one individual will have a single pimple and escape, while his fellow will find the first but the preparation of a long-continued series; or why some excess, like alcoholic overindulgence, will cause the appearance of a few passing pimples on one person's skin, while in another an acne once established becomes extensive and chronic.

With the guide of the opsonic index the phenomenon of auto-inoculation seems opened to satisfactory investigation in a manner heretofore impossible, for it is asserted that the specific immune opsonins of the particular active microbe respond in a characteristic and demonstrable manner under the impulse of spontaneous auto-inoculations; just as they vary and can be measured under the stimulus of the artificial inoculation of specific bacterial vaccine.

It has long been recognized that various extraneous influences modify the course of an existing infection. Upon a basis of such observations are founded various therapeutic practices, like the use of hot fomentations for regional inflammatory manifestations, of active or passive movement of inflamed joints, of massage, thermal or radiant treatment, and of passive hyperæmia by the method of Bier. Vigorous scrubbing with strong soap and hot water when directed against acne or furunculosis occasionally succeeds admirably, and so it is with the method still in vogue in some quarters, of forcibly squeezing and crushing the individual lesions in acne or furunculosis. Such occasional successes, terms of the new hypothesis, simply herald a favorable auto-inoculation produced by artificial means; the bacteria or their products being dissipated in such a manner as to reproduce what happens when a proper dose of corresponding bacterial vaccine has been inoculated.

Unhappily, however, there are many instances of effective or vicious auto-inoculation both spontaneous and artificial. Witness, for example, the steady downward progress of many a victim of chronic emphysema with all the manifestations of a continuous "negative phase." And how many melancholy cases the physician can recall of patients with pulmonary or joint tuberculosis, whose downward trend was precipitated by judicious exertion, or too energetic a treatment, massage, passive hyperæmia, or what not! On the other hand we have illustrated a spontaneous vicious auto-inoculation, and the other typifies vicious artificial auto-inoculation, in which exercise, massage, and induced hyperæmia are the artificial agents.

Artificial Auto-inoculation and Opsonic Diagnosis. Not only may the phenomena of spontaneous and a

ficial auto-inoculation be verified through the agency of the opsonic index, but, as now appears from the most recent contributions by Wright, the problem of the nature of an infection of unknown origin, or of the existence of a suspected but invisible local infective focus, may be solved. And, furthermore, diagnosis may not only be assisted by means of artificial auto-inoculation and opsonic evaluations, but aid in prognosis is also obtainable.

Given, for example, a case of chronic arthritis, whose bacterial factor is not clear and where the suspicion rests between the gonococcus and staphylococcus. The opsonic index for these two bacterial species would be taken with the affected joint at rest, and again at intervals of one-half, two to four, twelve to twenty-four, and thirty-six hours after massage, or exercise, or passive hyperæmia. The index for both organisms remaining practically constant throughout these examinations, one would rule out both bacterial species as responsible agents. But with a considerable fluctuation, say, of the gono-opsonic index, usually in the direction of a rise after artificial auto-inoculation, a diagnosis of gonorrhœal arthritis would be made.

Or let us assume that we have been treating a localized tuberculous lesion, and that the question arises as to whether success has been attained, and whether the infective focus is extinct. A tuberculo-opsonic index should be taken with the patient at rest, and again at intervals after artificial auto-inoculation set up by exercise, manipulation, or other suitable means adapted to the particular condition. An unchanged index would argue for recovery and freedom from restraint, while a fluctuation would justify the suspicion that a smouldering infection still persisted.

TECHNIQUE OF THE OPSONIC INDEX.—In the evaluation of the opsonic power of the blood comparison is made between the serum of the affected individual and that of one or several ("pool") presumably normal individuals. The value of a single serum, or, in other words, its capacity to stimulate phagocytosis, is termed its "phagocytic index." The comparison of the phagocytic index of a serum of unknown potency with the phagocytic index of one of several presumably normal serums, the value of the latter being taken as unity, gives the "opsonic index." Several steps are incidental to the procedure of measuring the opsonic index, as:

(a) *Collecting the Serum.*—One may select the lobe of the ear which is punctured, as in obtaining blood for hæmatological study, or the finger tips as the source of the blood whose serum is to be secured and tested. Children or nervous adults who dislike to witness the trivial operation of drawing blood may be accommodated by having their ear lobes punctured. But ordinarily the index finger is chosen, previously cleansed, and rendered hyperæmic by winding from its base to the last joint a narrow muslin bandage, or better still, a thin rubber bandage such as is used in Bier's method of producing passive hyperæmia. The congested finger tip is punctured at the side of the nail-bed with a lancet, or, as is done by Wright, with the sharp tip of the blood capsule.

The receptacle for the flowing blood is the ingenious blood tube or blood "capsule" of Wright, which is illustrated at actual size in several of his articles. It is a glass tube about 5 mm. in calibre, 6 cm. in length as ready for use, and with a capacity of some ten or fifteen drops of blood. It terminates by one extremity in a straight constricted point (the stabbing end), and at the other is drawn into a capillary, U-shaped tube. At the moment of collecting the blood both tips of the capsule are broken off, and the orifice of the U-shaped extremity is applied in contact with the escaping blood, which, in virtue of the capillarity of the U-shaped limb, is sucked through it and into the body of the capsule. As soon as sufficient blood to fill the capsule one-half or two-thirds has been automatically aspirated into it, the orifice of the straight end is sealed in a flame, the tube being grasped between thumb and finger in such a man-

ner as to insure no excessive heat reaching the column of blood. The vacuum occasioned by the cooling of the sealed end should suffice to draw the mass of blood into the capsule sufficiently far to empty the U-shaped extremity, by which the capsule is now grasped and sharply swung in such a manner as to drive the blood in mass to the closed straight end. At this stage of the procedure the tube is to be laid aside for the spontaneous contraction of the clot and separation of the serum, which can be hastened by incubator temperature; or it can be transported from the bedside to the laboratory. Finally the serum is separated by centrifuging, at a sufficient speed; the U-shaped end of the blood capsule serving as a handle by which it is hooked over the edge of the metal tube-shield of the centrifuge.

Both for separating the serum and for washing blood to obtain corpuscles one may employ a hand centrifuge, though more satisfaction will be experienced with a power centrifuge (electric or water, the latter operating well with compressed air when this is available).

(b) *Washing the Corpuscles.*—It is essential that human blood corpuscles, washed free from serum, be secured, for here we obtain the leucocytes whose phagocytosis is to be studied in the presence of various serums afterward added, along with the emulsion of the bacterium in question. For purposes of clinical usage the blood of any healthy person who is not fatigued may be used for washing. Preference is given to the finger tip, artificially congested by bandaging the member distally, as its source. One should stab beside the finger-nail so that, with adequate hyperæmia, large drops of the blood to the number of ten or fifteen exude and fall spontaneously from the finger-tip, rather than by coaxing with additional pressure or by applying the tube to the finger. These are the "honest drops" of the opsonist; and such honest drops to the number just indicated are allowed to fall directly into a narrow test tube containing 5 to 15 c.c. of a decalcifying (coagulation-preventing) normal salt solution, made by adding to 0.85 per cent. solution of sodium chloride in distilled water sodium citrate in the proportion of 1 per cent. As the blood drops into the tube of decalcifying solution it is gently agitated to effect an even distribution, until the requisite amount has been obtained. This mixture of blood and decalcifying fluid is now centrifuged at such a speed as to sediment the mass of blood corpuscles, but not with so excessive a rotation as compactly to jam the corpuscles to the bottom of the tube, resulting in the distortion or disruption of leucocytes. Properly performed this manoeuvre takes about five minutes, and drives the blood corpuscles out of the mixture in such a manner as to leave in the uppermost layer the majority of the white blood corpuscles, making the so-called leucocyte "cream." With a pipette of proper calibre the supernatant solution is now aspirated from the sediment of blood corpuscles, leaving them and their cream undisturbed. One washing, such as has just been described, suffices to free the corpuscles from their own serum, though for double assurance one may, after the first washing, perform a second with plain normal salt solution. For convenience the uppermost layer of corpuscles, or cream, is carefully aspirated and set apart for early use, before which it is gently agitated to insure an even mixture of its elements, consisting of the bulk of leucocytes from the sedimented blood mixed, of course, with red cells.

(c) *Making the Bacterial Suspension.*—This preparation consists of the bacteria against which the opsonic test is to be made, suspended in a normal salt solution, free from clumps of adhering microbes, and of such a density as to permit a sufficient, but to preclude an excessive, phagocytosis. That is to say, the suspension is to consist of isolated evenly distributed bacteria in proper numerical proportion. In working with dangerous bacterial species, e.g., the tubercle bacillus, the organisms may be devitalized by heat, though ordinarily this precaution is not taken. The technique of these suspensions varies somewhat according to the nature of

the particular microbe as to the coherence of the mass in culture, and the permanence of stainable forms. Thus with the pyogenic staphylococci the making of a smooth suspension by simple agitation and centrifuging is ordinarily an easy task, and these suspended cocci retain their staining capacity for at least two days. Tubercle bacilli, on the other hand, cohere most tenaciously, so that extreme efforts are required to obtain smooth suspensions, but they have the property of indefinitely responding to the appropriate stain. Gonococci and meningococci, because of their tendency toward self-digestion (autolysis), quickly cease to stain in a satisfactory manner, hence their suspensions must be made from young cultures on ascites-agar, and used without delay. With the exception of tubercle bacilli, gonococci, and meningococci, cultures on agar or coagulated blood serum (preferable for streptococcus and pneumococcus), of twelve to twenty-four hours' incubation, are used to prepare suspensions.

From the slanting surface of the culture medium the bacteria are washed by application of a few cubic centimetres of normal salt solution, the rough suspension being then withdrawn from the tube. Further mixture may be obtained by churning the suspension back and forth in a pipette, or it may be advisable to aid the process by rubbing the mixture between smooth glass surfaces or in a small agate or glass mortar. Additional dilution is now performed with 5 c.c. or 10 c.c. of normal salt solution and agitating. To throw out the coarse particles the suspension is now centrifuged, and if the supernatant suspension is still too dense, a further dilution and centrifuging may be performed. A proper density of the suspension is important, for if too large a number of the bacteria remain, the phagocytosing leucocytes become overloaded, making enumeration difficult or impossible. To obviate this drawback one may count the bacteria in the suspension (see below, Standardizing Bacterial Vaccines) or, better still, preliminary opsonic tests with normal serum and washed corpuscles can be performed, in order to obtain a phagocytosis averaging five to ten pyogenic bacteria (the pyogenic cocci, colon and typhoid bacilli) per leucocyte, and one or two tubercle bacilli per leucocyte.

(d) *Preparing Suspensions of Tubercle Bacilli.*—Wright uses the bacillary mass from surface glycerin-broth cultures of tubercle bacillus, or the residue after making old tuberculin. In my own work I have found the surface growth on glycerin-agar to answer well. The mass of bacilli is freed from fluid by paper filtration, washed on the filter paper, first with water and then with 1.5 per cent. salt solution, and divided into smaller portions which are subjected to streaming steam or autoclave sterilization in suitable small flasks for three successive days. A globule of the bacillary mass not larger than a split pea is now rubbed with 1.5 per cent. salt solution until smooth. One or two drops of the salt solution moistens the mass, followed by grinding for ten minutes, then drop by drop, with intervening rubbing, the salt solution is added until 1 c.c. has been reached. This coarse suspension is transferred to a small narrow tube and centrifuged at high speed for five minutes or longer. The supernatant suspension is now subjected to an opsonic test with normal serum and washed corpuscles. If the bacilli are evenly distributed and free from clumps, and the phagocytosis is more than one or two per leucocyte, the supernatant suspension is separated and kept as a stock which is diluted at the moment of using so as to bring the phagocytosis to the required point as determined by a test. Such a stock suspension may be kept in the cold, and is available for at least a week. The original masses of sterilized culture should be kept moist in the small flasks, and are useful so long as in this condition.

(e) *Mixing Serum, Washed Corpuscles, and Bacterial Suspension.*—A mixing pipette or opsonic pipette is required for this operation. As used by Wright and his followers this implement resembles an ordinary glass medicine dropper with a much elongated narrow ex-

tremity. The body of the pipette is a tube 5 cm. and about 6 mm. in diameter. Its elongated extremity measures 10 cm. to 15 cm. and has a calibre of about 1 mm. to 0.8 mm. For aspirating the components of mixture one may employ the ordinary rubber bulb test used with medicine droppers. A more satisfactory device for preventing excessive suction is a rubber bulb operated with a small Hoffman's tubing clamp, or rather elaborate apparatus in which a graduated scale makes pressure on the rubber diaphragm of an chamber.

About 1 or 2 cm. from the attenuated extremity of pipette a "fiducial" line is made with a wax pencil and ink. The serum reposes in the capsule after having been centrifuged, and is most readily expressed by crushing the capsule at the desired point with a pair of old bone-cutting pliers. A convenient receptacle for the capsules, tube of washed corpuscles, and tubercle bacterial suspension is a dish of wet sand. Having these in readiness the procedure is to draw to the mark on the pipette a portion of the washed leucocyte cream, then aspirate a short column of air; then draw to the mark a portion of the bacterial suspension; now follow with a dividing column of air; finally aspirate to the mark a quantum of the serum to be tested. The equal portions are now to be mixed by forcing them out of the pipette on a clean slide, drawing in and forcing out again. The mixture, without air bubbles, is finally drawn into the pipette, the free extremity of which is sealed in a flame, and the whole is ready for the incubator.

(f) *Incubating the Mixture.*—To facilitate the opsonic process and phagocytosis the mixture in the pipette is kept at a temperature of 37.5° C. for fifteen or twenty minutes. The pipettes may be placed in an ordinary incubator held in a pasteboard or metal rack, or the special opsonic incubator of Freeman, consisting of a cylindrical water-bath with automatic temperature regulator tubes for the pipettes, may be used. Since the serum suspension, and corpuscles tend to separate, it is well to agitate the pipette gently once or twice during incubation, or recourse may be had to a mechanical device by which the tubes are rotated with a small pulley operated by a miniature water or electric motor.

(g) *Preparing, Fixing, and Staining the Film.*—After incubation the end of the opsonic pipette is broken and its contents are mixed by forcing onto a clean slide drawing back into the pipette. A drop of the mixture suitable in size is now placed near one end of a clean microscopic slide and spread as in making a blood film, except that the spread is thicker and is purposely not somewhat uneven. A special "spreader," consisting of a slide from one end of which the corners have been cut across or ground off, is used for making a film thinner than the slide, thicker at the starting-point, tapering, tongue-like and thinner, as the spread proceeds.

In the case of tuberculo-opsonic preparations, and to insure a smooth film free from alternate heaps and deserted areas, some workers prefer a slide the concave surface (found by testing the slide on a perfectly smooth surface) of which is roughened by rubbing with emery paper.

The dried films in the case of ordinary bacteria are fixed by flaming; or, as is the writer's practice, fixed and given the plasmatic stain by treating with alcohol and eosin solution.

Films for tubercle bacillus preparations are to be fixed in saturated watery solution of corrosive sublimate about one minute, or by immersion in wood alcohol several minutes; or one may flood with ordinary alcohol and ignite it, thus combining alcoholic hardening with heat fixation.

Staining of the films, except in the case of tuberculo-opsonic preparations, is performed by the aid of eosin and methylene blue. Various formulas in which tannin and anilins are combined in a single solution like Leiman's or J. H. Wright's stains, can be employed,

the operations performed according to the usual directions for staining blood preparations. Or the eosin and blue can be used separately, as is the writer's practice; alcoholic eosin (eosin, alcohol-soluble, Grüber, one per cent. in ninety-five per cent. alcohol) is first applied to fix and stain the film, which is next washed in water and then stained with a one-per-cent. solution of methylene blue (preferably the methylene blue after Ehrlich, of Grüber). After staining, the films are dried and mounted in balsam, or examined in oil with the oil immersion lens, without covering.

Tuberculo-opsonic films are first stained in hot carbol-fuchsin several minutes, washed in water, decolorized in two-and-one-half-per-cent. sulphuric acid aqueous mixture a few seconds, washed in water, further treated with five-per-cent. acetic acid for a few seconds, washed thoroughly, and counterstained a few seconds with methylene blue (1 gm. rubbed in 1 c.c. absolute alcohol, to which "mud" is added 200 c.c. of a 0.1-per-cent. solution of sodium hydrate, and the whole filtered). This is the method advised by A. E. Wright.

(h) *Counting and Determining the Index.*—With the low power of the microscope the finished opsonic preparation is scanned, and the area in which the white cells are numerous, generally the ends of the film, is located, whereupon the immersion lens is focussed. The next task is to count the bacteria englobed by the polynuclear leucocytes, so as to strike the average. With the pyogenic bacteria it is generally sufficient to count the bacteria in twenty-five white cells, but with tubercle bacilli fifty to one hundred cells are included in the count. The average per leucocyte obtained by these counts gives the phagocytic index for the serum under observation. To obtain the opsonic index a control preparation, with individual normal serum or pooled normal serums, is simultaneously carried through all the stages just described.

The phagocytic index of the normal serum is obtained by the same count and average as for the serum in question. The opsonic index represents the ratio which the phagocytic indices of the two serums bear to each other, the phagocytic index of the normal serum being taken as unity. It is obtained by the following proportion—the phagocytic index of the normal serum: the phagocytic index of the serum in question :: 1 : x . For example, assume that the staphylo-opsonic index is to be obtained, and that the average staphylococci per leucocyte, or the phagocytic index of the normal serum, is found to be 16; and the phagocytic index of the serum in question to be 12. The proportion would be 16 : 12 :: 1 : x ; and the opsonic index, $\frac{3}{4}$ or 0.75.

TECHNICAL MODIFICATIONS OF THE OPSONIC INDEX.—It must not be assumed that the method of Wright and Douglas for obtaining the opsonic index has been accepted unchallenged by laboratory workers. There are, indeed, those who claim that the results are far from reliable, due to various faults in the method; and others who vigorously insist that the opsonic index is not a reliable guide upon which to base therapeutic bacterial inoculations. But aside from these controversial aspects, certain modifications in the technique have been proposed.

By some workers Leishman's original method is still adhered to. This consists in using the whole blood, equal portions of which and of the bacterial suspension are mixed, a drop of the mixture placed on a slide, covered with a cover-glass, and incubated for ten or fifteen minutes. The slide and cover are then drawn apart, the film is stained, and the phagocytic index is computed as described above.

Other workers have aimed to reduce the experimental error by employing highly dilute suspensions of bacteria; or, better still, by diluting the serums under scrutiny. Combined with the modifications of diluting the suspension and the serum is the suggestion to use as a basis of comparison the phagocytizing leucocytes, giving a so-called "percentage" index as opposed to Wright's "bacterial" index.

The Thermostable Opsonin Test.—An outgrowth of further investigation into the properties of opsonins is the application of the opsonic index to the diagnosis of existing infection, as well as in the study of immunizing reactions following bacterial inoculations or artificial auto-inoculation. The principle of this diagnostic procedure which has been developed by Wright and Douglas, and by them designated the "thermostable opsonin test," rests upon the study already alluded to of the variation in heat resistance between the common opsonins and the immune opsonins. Representatives of the latter class are less easily destroyed by heating, that is to say, they are thermostable opsonins. Accordingly, if the problem is to determine whether a given bacterial infection exists in virtue of which immune opsonins are being produced by auto-inoculation, or to learn if a bacterial inoculation has aroused specific immune opsonins, the procedure is to heat the serum in question not less than ten minutes at a temperature of 58° to 60° C., and then measure its opsonic power by the phagocytic index as ordinarily obtained. Granting the accuracy of the observations upon which this test is founded, it would be proper to recognize the opsonins which survived this heating as resulting from auto-inoculation with the corresponding microbe, or, in case of the inoculation of a vaccine, to represent the immunizing response in production of immune opsonins. Thus the thermostable opsonin test serves as a further check upon the method just described, in which the testing of the opsonic power of the blood can be brought to play a part in the diagnosis of a suspected bacterial infection, or to allow the identification of the specific bacterial nature of an infection whose existence is evident.

PREPARATION OF BACTERIAL VACCINES.—"Vaccines," or the special bacterial substances used in opsonic therapy, are of two classes: *corresponding*, that is, identical in species with the pathogenic microbe against whose inroads effort is directed; and *autogenous*, as the writer has called them, that is, of bacteria obtained directly from the infected individual and reintroduced for therapeutic purposes. Corresponding vaccines are also designated "stock" vaccines. As to the particular merits of these two classes of vaccines, evidence is still insufficient to permit final judgment; though enlarging experience in opsonic therapy seems to indicate that with few exceptions better results, and in many cases satisfactory results alone, are to be obtained by the vaccine made from the microbe of autogenous origin, subjected to as little artificial manipulation as is possible; that is to say, the microbe reintroduced in as near its original biologic condition as laboratory manipulation will permit. Subcultivation, by which many pathogenic bacteria speedily lose the properties incidental to their habitat in the morbidly affected animal organism, is to be minimized. It appears that, in the case of certain staphylococci, the changed environment of repeated transfer on artificial culture media does not deprive them of usefulness in the production of stock vaccines directed against some forms of staphylococcal infection; though no one has learned whether the full remedial property of a staphylococcus artificially grown is retained, or, if lost, when. Obviously, autogenous vaccines are imperatively required when one encounters, in an infection of unknown origin, one or more of the less common bacterial species like *Bacillus mucosus capsulatus* and the pseudodiphtheria bacillus; or in the case of such groups as the streptococci, colon-paracolon, and proteus in which variation is an outstanding characteristic. Likewise in mixed infections where several bacterial species are simultaneously encountered, and against all of which combat is required, it would be practically impossible to have in stock the appropriate corresponding vaccines, even if there was reason to believe these ready-prepared products might be effective; and this objection would hold good in those not rare instances in which, during the treatment of a chronic infection, the bacterial flora changes.

There seem to be, indeed, most weighty arguments

in favor of employing autogenous vaccines made from freshly isolated bacteria, and for stock vaccines of the trade no argument whatever save commercial expediency. For clearly one who is sufficiently skilled to practise opsonic therapy safely and intelligently is assuredly competent to prepare his own vaccines; and he whose knowledge and skill preclude his isolating, identifying, and making into a vaccine the autogenous microbe is incompetent to practise therapeutic inoculation even with stock vaccines.

(a) *Suspension or Emulsion of Bacteria*.—In a general way the process of preparing a bacterial vaccine is identical with that described under bacterial suspensions for use in determining the opsonic index. At least this holds good for the preliminary stages in which the bacteria are cultivated in tubes of solid media, washed off in sterile salt solution, and shaken or churned to effect separation of the component organisms. Ordinarily it is sufficient to use 5 c.c. of salt solution in preparing this first suspension, and, unless there is marked persistent cohesion of the bacteria in masses, centrifuging of the suspension is superfluous. This first suspension or unstandardized vaccine is transferred to a suitable sterile receptacle—a test tube, for example, which may or may not be hermetically sealed. A drop of it is withdrawn and set aside for standardizing. The rest is now to be heated to devitalize the bacteria, which is accomplished by immersing the container with crude vaccine in a water bath, the temperature of which is kept at 55° to 60° C. The duration of this devitalizing process varies somewhat according to the varying thermal death-point of the bacterial species in hand. One hour at 60° C. is an outside limit. Most pyogenic microbes in the vegetative form, as called for in preparing these vaccines, succumb in one-half hour's heating at 60° C. Gonococci and meningococci yield at a temperature of 55° to 58° C., and usually in ten minutes. As a further precaution, particularly when one is obtaining early familiarity with this step in opsonic technique, it is wise to plant a small portion of the heated vaccine as a control culture to test its sterility.

Returning now to the culture whose bacteria furnish the material for the vaccine, some further points may with value be elucidated. For the more usual and easily grown species plain agar or glycerin-agar is the medium of election, but here as elsewhere in which solid culture media are called for in opsonic practice, it is highly desirable to have the medium moist and supplied with a moderate amount of water of condensation. A growth of twelve to twenty-four hours' incubation is sufficient. Gonococci and meningococci are grown on ascites-agar or ascites-glucose-agar for eighteen to thirty-six hours. Streptococci and pneumococci grow most luxuriantly on Loeffler's blood-serum mixture, and require twenty-four to forty-eight hours' incubation. This same medium answers well for the meningococcus and for some strains, at least, of the gonococcus.

The pus or other exudate containing the infecting organism is smeared upon the surface of the solid culture medium. Should there be reason to believe that but a single bacterial species is present in the material, e.g., staphylococcus in the pus of an acne pustule, or in that from a boil or carbuncle, no necessity will arise for making dilutions and plate cultures; instead, the primary culture as it appears on the surface of one or more tubes may be used to prepare the vaccine. Or, should the single colonies of a single species be widely isolated on the first tube or tubes after twenty-four hours' incubation, they may be spread to produce a growth sufficiently extensive to cover the surface of the culture medium and allowed an additional incubation of twenty-four hours.

In anticipation of infection with mixed bacteria the handling of the original material is such as to allow of the separation and identification of the various species. Most opsonists resort to plate cultures with the aim of meeting this contingency, and occasionally this too complicated process is the only one that will answer. From a considerable experience, however, the writer

has found that the much simplified method of Baggins will generally suffice for separating so as to secure in pure culture the various bacteria constituting the flora of a mixed infection. This method, it may well to remind the reader, is one in which ordinary slanted medium in a test tube is required, and dilution is effected by bringing the loopful of exudate into the condensation water of the first tube, where it is mixed thoroughly. After flaming the loop it is used to carry one or two loopfuls of infected condensation water to the water in tube two, and the manoeuvre is again repeated by carrying from tube two to tube three. The infected condensation water in the three tubes is now allowed to flow over the surface of the medium, the tubes containing which are then returned to an upright position, and placed in the incubator, where, usually the second, and almost invariably in the third dilution, well-isolated pure colonies will arise after the proper interval. Should media without condensation water alone be available, separate colonies often can be secured by rubbing the loopful of exudate over the surface of the tube, and then, without flaming, over the surface of the media in the second and third tubes; or a series of parallel "scratches" may be made with the loop containing the exudate, beginning with the first tube, and, after the surface has been covered with longitudinal striations proceeding in the same manner with the second and third tubes. In isolating streptococci, pneumococci and meningococci, Loeffler's medium in slants is most satisfactory and may be used in a single implantation or by the Baggins-Groszlik method in case mixed infection is suspected. In the case of the meningococcus it is well to know that this organism sometimes appears tardily, and one should not pronounce negatively upon the culture until at least a week has elapsed. Gonococci are most expeditiously isolated from the pus of a fresh untreated urethritis, and here one may profitably resort to ascites-glucose-agar in Petri plates, smearing the pus over the surface by the "scratch-culture" method as just described.

Having isolated and identified the species in a mixed infection, the opsonist is confronted with the question to which species, or whether all, are to be converted into vaccine and used for inoculation. This is largely a matter of bacteriological judgment and of experience in opsonic therapy. Thus, if more than one variety of given species, as, for instance, *Staphylococcus albus* and *S. citreus* from acne pus, is encountered, it would be entirely proper to use a vaccine composed of a mixture of both varieties. Again, in the event of a mixed flora with one well-known pathogenic species predominating, this would naturally be chosen; or if two well-known but distant pathogenic species were prominent, like *Streptococcus* and *Bacillus pyocyaneus*, vaccines from each would be employed. However, it may befall one particularly in treating old suppurative lesions like sinuses, fistulas, empyema, etc., to ignore an organism like one of the proteus group, or a member of the coliform group, that at first blush would be regarded as a saprophyte, and by thus failing to employ its vaccine along with staphylococcus, streptococcus, or other acquaintances among the pyogenic bacteria, to meet with poor results.

Furthermore, there is always to be kept in mind, especially in treating chronic suppurations, the possibility of a changing bacterial flora in the course of the treatment. In the writer's experience, to cite one of several examples, what originally responded as an unhealed empyema due to unmixed *Pseudodiphtheria bacillus* infection, in later culture showed an admixture of *Staphylococcus aureus*, later the unmixed *aureus*, and finally the pneumococcus, inoculations with the changing autogenous bacteria, were imperatively required to effect the desired improvement.

(b) *Standardizing the Vaccine*.—The drop of the original suspension removed before devitalizing the bacteria in a vaccine serves for standardizing, which is effected by counting the bacteria in this original suspension

which is then diluted so as to secure the proper dosage when subdivided. Counting the bacteria in a given suspension is performed after the method proposed by Wright and best described in his own language, in which he is concerned with the standardizing of a typhoid vaccine, but which applies equally well to suspensions of the usual pathogenic bacteria. He says: "This enumeration can in the case of a twenty-four- to forty-eight-hour culture of the bacillus typhosus be made in an accurate and expeditious manner under the microscope. It will be manifest that in the case where we are dealing with a mixture of an aliquot volume of normal blood (containing 5,000,000 red blood corpuscles per cubic centimetre) with an equal volume of bacterial culture, the number of micro-organisms and red blood corpuscles in a film prepared with such a mixture will stand one to the other in a ratio which corresponds to the respective numbers of red corpuscles and bacilli in the unit of volume.

"The mixture of the blood and culture in definite proportions is made as follows: We take in hand an opsonic pipette. Having placed a mark upon the capillary stem at a convenient distance from its orifice, and having by means of the teat established a negative pressure in the interior of the tube, we draw up in succession into the capillary stem (a) one volume of blood (obtained from a prick in the finger) such as will fill the capillary stem up to the fiducial mark; (b) an air bubble to serve as an index; (c) a volume of the vaccine; (d) and further three volumes of a physiological salt solution; or, in lieu of these last, as may be required, one, two, or three further volumes of the vaccine; taking care to complete in each case to five volumes. Having expelled the contents of the tube on to a slide, and having effected thorough mixture by drawing up the fluid into the capillary pipette and blowing it out several times in succession, we transfer a drop of the mixture to a microscopic slide and spread it out by bringing down upon it the edge of another slide and drawing this along. The thickness of the film is regulated by adjusting the angle between the slides, widening this angle when a thicker film is to be left behind, and narrowing it when a thinner film is required. The film is then fixed and stained, most conveniently, perhaps, by the stain described by Leishman. The bacteria and red blood corpuscles are now separately enumerated on a series of fields chosen at random from different parts of the preparation. Owing to the spacing out which is secured by the five-fold dilution of the blood, this enumeration can, if necessary, be carried out without restricting or subdividing the field of the microscope. It, however, facilitates matters if we restrict the field by the employment of a high-power eye-piece and subdivide it by inscribing a cross by means of a glass writing pencil upon a cover-glass, and dropping this into the eye-piece. The necessary calculation can be most easily carried out by the help of a slide rule.

"Suppose we have a typical field of such a film preparation as has been described above. It will be found that there are here contained in this field of view thirty-six blood corpuscles and twenty typhoid bacilli. Making the assumption that we are here dealing with a normal blood and, as already postulated, with an average field, the calculation we make is as follows:

"Number of red blood corpuscles in average field : number of bacilli in average field :: number of red blood corpuscles in the unit of volume : number of bacilli in the unit of volume.

"36 : 20 :: 5,000,000 : (number of bacilli in the cubic centimetre of culture). Answer: The culture contains circ. 2,800,000 typhoid bacilli in the cubic centimetre.

"In the case where, in lieu of 1 volume, 2, 3, or 4 volumes of culture have been mixed with one volume of blood, the number of bacilli in the cubic centimetre of culture will of course correspond to the quotient obtained by dividing the result arrived at in the above calculation by, as the case may be, 2, 3, or 4."

(c) *Tubercle Vaccine*.—Although some attempts have been made in that direction, the production of an autogenous vaccine from a given case of tuberculous infection has thus far been attended with indifferent success. That this should be so is readily appreciated by those familiar with the biological peculiarities of the tubercle bacillus, and who recognize the great technical difficulties involved in the attempt to secure this organism in pure culture, especially when, as is so often the case, it is present in lesions associated with other bacterial species. Furthermore, the comparatively slow growth of this microbe is a drawback to its use for an autogenous vaccine, and when recourse must be had to the indirect method of guinea-pig inoculation and subsequent recovery in culture, one naturally hesitates about using the bacillus so recovered because of the possibility that its sojourn in the guinea-pig might have sufficiently changed it so as to be unfit for therapeutic use in man. In any event, the custom is to resort to one of the several tubercle-bacillus preparations already in use; though here, too, it must be confessed, we are still ignorant as to the source of the organism employed, or as to what has befallen that particular organism in the way of artificial cultivation after its isolation.

Wright usually advises the use of Koch's new tuberculin (T. R.) which is practically a suspension of tubercle bacilli in which the residue, after washing in water by the centrifuge, forms the basis. This preparation is dispensed in bottles, the menstruum being a forty-per-cent. glycerin mixture with a bulk of 1 c.c., and holding in suspension after shaking, 10 mgm. of the tubercle bacillus powder. Another preparation which has preference with some workers is that form of Koch's new tuberculin (B. E.), the bacillus emulsion, which has as a basis tubercle bacilli previously subjected to grinding, without washing, suspended in a glycerin menstruum, and dispensed in glass-stoppered amber bottles in which 5 mgm. of the bacillary powder is present in 1 c.c. of the fluid. As employed in opsonic therapy special precautions are taken in the dilution and preparation of these tuberculins, and the following description modified after Wright, and specifically concerning T. R., is also applicable to B. E., except that the computation is made for the latter on the basis of 5 mgm. of solid substance instead of 10 mgm. as for T. R. Since the dose of these tuberculins commonly employed is from $\frac{1}{1000}$ mgm. to $\frac{1}{100}$ mgm., it is clear that the original product must be largely diluted.

An original sealed bottle of T. R. is procured, well shaken, and opened with care to prevent contamination, either by cautiously flaming the neck and stopper or by immersing the whole container in pure lysol for a short time, afterward wiping with sterile gauze or towel. Aspirate the original T. R. into a sterile pipette of adequate size; seal this in the flame; wash out the container with 1 c.c. of sterile salt solution which is aspirated into a second pipette, sealed, and, with the one already filled, placed in a water-bath and heated one hour at 60° C. This precautionary additional sterilization of the tuberculin recommended by Wright may be performed by immersing the original unstoppered bottle in water sustained at 60° C. for one hour, after which it is to be handled with precaution to avoid contamination, such as would be used in an aseptic operation. The most convenient container for the tubercle vaccine is the vaccine bottle of Wright, wide-mouthed, of amber glass, fitted with a thick rubber cap, and of a capacity of 50 c.c.; but of course any suitable sterilized flask or bottle may be employed. Into the sterile vaccine bottle, filled with 48 c.c. of sterile normal salt solution to which lysol in the proportion of 0.25 per cent. has been added, the contents of the two pipettes is forced. This step is conveniently performed by drawing to a fine point the sealed ends of the pipettes, which are then broken, and plunged through the rubber cap of the vaccine bottle, to which cap lysol has previously been applied; after which the tuberculin is expelled. This first dilution, or "concentrated vaccine" contains $\frac{1}{2}$ mgm. of tubercle

bacillus powder to each cubic centimetre. The second dilution for daily use is made by adding $\frac{1}{2}$ c.c. of concentrated stock to 50 c.c. of normal salt-lysol solution in a second vaccine bottle; and this, the finished tubercle vaccine, contains $\frac{1}{10}$ mgm. of tubercle powder, so that each cubic centimetre of it equals $\frac{1}{10}$ mgm. of T. R.

INFECTED TISSUES AND EXUDATES AS VACCINES.—Precedents for the use of infected-tissue substances or of the exudates arising from infection as vaccines for protective inoculation were established long before the practice of therapeutic bacterial immunization based on the theory of opsonins came in vogue. Thus the virus of vaccination against smallpox is the exudate of the lesions of vaccinia. In hydrophobia the principally affected tissue (spinal cord) of the rabbit infected with rabies supplies the material for the vaccines. And in symptomatic anthrax vaccines are prepared from the dried powder of the muscles of cattle recently dead of "black leg." In each of these cases it is assumed that the tissue or exudate also contains the infectious agents, which in the case of variola and hydrophobia still remain unidentified.

From the use of such morbid material for protective inoculation, variously modified to attenuate its original virulence, to the use of similar products with the object of inducing a curative immunity was a reasonable step; and it accordingly is not surprising to find that experiments in this direction have been recently revived. One such essay was to treat a purulent empyema by the subcutaneous injection, into healthy tissue, of the pus aspirated from the affected pleural sac, the results of which are asserted to have been satisfactory from a therapeutic standpoint. Another was the use of material from caseous tuberculous glands, sterilized (?) by exposures to low temperatures, as a therapeutic vaccine for tuberculosis, and here the outcome is said to have justified the continuation of the method. Still more recently, the exudate from a lumbar puncture in an individual with acute cerebro-spinal meningitis has been subcutaneously injected in the original patient, or in others afflicted with the disease, apparently with favorable results. It is still too early to speak with assurance as to the promise for this kind of modified therapeutic immunization, which may be classified as another method of artificial autoinoculation. But in view of what has been accomplished by therapeutic inoculations of dead pathogenic bacteria, it is not difficult to believe that a combination consisting of the infectious agent modified by its sojourn in its host, and of the diseased tissues or juices of that infected host, possesses the power of arousing specific curative immunizing impulses, and perhaps to a degree unattainable by the use of devitalized bacteria cultivated on artificial media. But the obstacles in the way of a standard for dosage are, among others that readily suggest themselves, at present so great that this work can only be viewed from an attitude of hopeful expectancy; though it must not be forgotten that the discovery of vaccination for smallpox came through an accident, and that even to this day there is no exact standard of dosage of the antivariolous virus.

TECHNIQUE OF BACTERIAL INOCULATION.—*Dosage of Bacterial Vaccines.*—No hard-and-fast rules can be formulated to govern the dose of bacteria in a given vaccine as directed to the treatment of a certain infection. Individual difference in immunizing response, and variation in the properties of various bacterial species, or "strains" of a given species, are two of the several factors which are to be considered in deciding the question of dosage. Only the rough general figures indicated by Wright and others with large experience in bacterial inoculation can be offered for preliminary guidance, from which departure will be indicated either through failure to secure a satisfactory effect as demonstrated by the fluctuation of the opsonic index in the event that this test is relied upon for guidance, or through unsatisfactory symptomatic reaction as shown by too severe a local irritation at the injection point, and too pronounced a constitutional negative phase (languor, chilli-

ness, fever, headache, and depression); together with an unsatisfactory amelioration of the particular morbid condition against which the treatment is directed.

With the qualifications just indicated, it may be stated that the dose of pyogenic staphylococci varies from 100 million to 1 billion; of streptococci and pneumococci from 5 million to 50 million; of gonococci 10 million to 50 million; of meningococci 5 million to 50 million; colon bacilli 25 million to 200 million, beginning with small dose as severe local and general reactions sometimes attend the inoculation of this organism; of *Bacillus pyocyaneus*, *B. pseudodiphtheriae*, *B. proteus*, and *B. mucus capsulatus* 50 million to 200 million; and of *Micrococcus neoformans* 50 million to 200 million. Tuberculin is administered in doses of $\frac{1}{1000}$ to $\frac{1}{500}$ mgm. T. R.

Method of Inoculation.—Bacterial vaccines are administered solely by subcutaneous injection. The most convenient instrument for this operation is a glass syringe with asbestos-packed plunger and a capacity of not more than two cubic centimetres. Vaccine should be preferably so standardized as to contain maximum dose in 1 c.c. of fluid, or to be even more concentrated so that a fraction of a cubic centimetre may be taken, and raised to a bulk of 1 c.c. by addition of lysolized ($\frac{1}{2}$ per cent.) sterile normal salt solution at the moment of using. The needles should be somewhat larger than those of the ordinary hypodermic syringe.

To sterilize a syringe recourse may be had to a five-per-cent. aqueous lysol mixture. Better still, the syringe, plunger, and needle may be boiled in slight alkaline water, though this is destructive of needle. If the hub of the needle be provided with an asbestos washer, or if union of syringe barrel and needle is made by a ground joint, sterilization is most expeditiously performed by following Wright's direction to draw into the syringe several charges of oil (olive oil or, better still, fluid vaseline) which is heated to 130° C.; but with ordinary rubber washers to complete the joint of the syringe barrel and needle hub this procedure is impracticable, because of the injurious action of the hot oil on the rubber.

Injection is to be strictly subcutaneous, which means that it must not be made so superficially as to separate the skin itself and raise a wheal, nor deep enough to enter the muscles. The subcutaneous fascia, or the subcutaneous fat, is the layer into which the vaccine is to be directed, both because the effects are more comfortable for the patient, and principally because it appears that the connective tissue is the tissue in which the production of protective antibodies goes forward most satisfactorily. The skin at the point of inoculation may be cleaned with alcohol, or puncture may be performed through a spot wet with pure lysol which is to be wiped off with alcohol. But in clean persons these precautions are superfluous.

Injection Site.—The choice of the location in which inoculation is to be performed may or may not be a matter of importance. As a rule, the site of election is the flanks, the anterior abdominal wall, or the interscapular region, particularly if a generalized infection is to be treated, or if, as in facial acne, inoculations in the neighborhood of the lesions are undesirable. But with sharply localized infections so situated as to allow inoculation into a site whose lymphatic drainage passes through the diseased areas, it is good practice to proceed with this object in view. Thus in infections in the extremities, in either soft parts, or bones, or joints, it is well to inoculate in a point beyond, or situated distal to, the lesion; and by observing the trend of lymphatic drainage in the trunk, injection may often be performed so as to flood a localized lesion directly from the inoculation site.

Not less important than the question of site is the precaution that should be taken against repeated inoculations in a given locality; for since the immunizing reaction is supposed to spring from the connective tissue of the inoculated area, it is reasonable to presume that

the capacity of a given tissue area to react may be worn out by too frequent an injection.

No dressing is applied to the inoculated site, and it is not desirable to seal the minute puncture made by the needle. The redness and swelling that sometimes follow a large dose of bacterial vaccine require no treatment. Occasionally, especially after repeated inoculations, indurations remain in the subcutaneous tissue. Should these appear, it is well to suspend injections until, by gentle and repeated massage, the nodules have disappeared. With properly prepared vaccines, administered in correct dose, and with sterilized injection apparatus, abscesses at the inoculation site should never appear, even though a sharp local inflammatory reaction at times is provoked.

Interval between Inoculations.—Next to the question of dosage of bacterial inoculations comes the important consideration of their periodicity. Where the opsonic index is employed as a guide, Wright's original rule of a new inoculation when the positive phase of the preceding one has reached its height, or is just beginning to fall, should be followed; as should also his injunction not to repeat the inoculation during the original negative phase. Again, where the effects are outspoken, as at times they are both in the local lesion and in the constitutional symptoms, it is quite easy, with the aid of an intelligent subject, to space the inoculations so as to repeat the injection before, or immediately after, the positive phase subsides. But there are times when the opsonic index does not pursue a characteristic course, and more often still comes the difficulty of taking an accurate index sufficiently often to be of service; and local and symptomatic responses may be slight or absent after some inoculations, so that the opsonist is confronted with the problem of spacing his injections according to some cut-and-dried rule. Such rough rules have been formulated and will serve the beginner until his experience has enlarged to a point at which it becomes his best guide. For example, inoculations for generalized infections like septicæmias are performed at intervals of one to three days, especially on the occasion of the earlier ones. In rapidly spreading acute infections like endometritis, cellulitis, and lymphangitis, inoculations should also be spaced at intervals of one to three days until the urgent period has passed. Subacute and chronic localized staphylococcal diseases like acne, furunculosis, and eczema are to be treated every five to seven days. The same interval seems well suited, especially during the earlier inoculations, to the handling of chronic suppurative lesions of varying bacterial origin like old empyemas, sinuses and fistulas, middle-ear disease, antrum disease, and bronchitis. In tuberculosis it is customary to employ the tuberculin every ten to fourteen days, and where a mixed pyogenic and tuberculous infection exists it is good practice to inoculate with the pyogenic bacteria every five or seven days, adding the tuberculin on the occasion of each second injection.

Mixed Infections.—What should be the course in case of a mixed infection? Here, as elsewhere in the practice of bacterial therapy, judgment as to the relative importance to attach to the various factors must decide the question. Given two or even three bacterial species, well known as pathogenic agents, and their simultaneous appearance in the secretion of a certain lesion, it is entirely proper, as has already been intimated, to inoculate a mixed vaccine containing suitable doses of the offending bacteria. Or when the urgency is not too great, inoculation with the predominating and most likely pathogenic agent is to be first performed, and, in case of an unsatisfactory issue, a vaccine from the other bacterial species can be added in subsequent injections. Say, for instance, that *Staphylococcus aureus* or a streptococcus is found associated with *Bacillus coli* in the discharge from fistulas of abdominal origin, a mixed vaccine would be in order. Again, especially in old suppurative lesions, a putrefactive organism (of the proteus group generally) is found largely exceeding the under-

lying and presumably original pyogenic agent like staphylococcus or streptococcus. Here the pyogenic microbe might first be tried, but to it should be added a vaccine from the secondary organism in event of its failure to bring a good result. It is well to repeat how surprising it is at times to find that success depends on the use, in conjunction with the vaccine of a well-known pathogenic species, of that prepared from the secondary invader belonging to the proteus-like, or colon-like, or pseudodiphtheria-bacillus group.

The Reaction of "Hypersusceptibility."—With recently acquired information concerning the peculiar reaction to proteid injections, first clearly brought out in connection with the use of horse's serum by v. Pirquet and Schick in their studies of the "serum diseases," it is quite natural to look for some manifestations of a similar nature following the periodic injection of bacterial vaccines required in opsonic practice. In my own experience I have observed on several occasions, in certain patients, immediate symptoms like flushed face, dizziness, and nausea when inoculations were repeated, which could be explained only on the basis of their being a mild manifestation of the phenomenon of proteid hypersusceptibility. No unpleasant consequences followed these temporary symptoms, which, in a very considerable number of cases, were so rare as to be quite exceptional. Very rarely, also, temporary skin eruptions like the "serum rashes," or attacks of itching, will appear after repeated inoculations.

Blood Coagulability as Related to Therapeutic Immunization.—Infection modifies the blood-clotting power, and it often becomes important to scrutinize this property of the blood during the course of therapeutic bacterial inoculations, which in themselves modify the coagulability of the blood. Generally Wright's simple time test, with the blood drawn into a fine tube and blown out at intervals of one-half minute, suffices to give a working idea of the coagulation time. In certain chronic pyogenic infections the blood-clotting power will be found persistently low, and should a wound and discharge be present, the wound will usually be excessively moist, and the discharge thin and abundant. Other manifestations of low blood-clotting power may also be in evidence, like localized oedemas or watery diarrhoea. Should inoculations fail to correct these symptoms the use of calcium, preferably in the form of calcium lactate in 10-grain powders, dissolved in hot water, at first three times daily and later once a day, will be found very beneficial.

In contrast to the state of lowered blood coagulability is that of excessive clotting power, also met in connection with some infections. There may be, for example, a localized infection with much induration, diffuse inflammation, and a dry non-secreting state of the tissues, the so-called "brawny swelling" of English surgeons. Here a coagulation test usually shows increased activity. Again, the infection may be accompanied by intravascular coagulation and the formation of thrombi. Both of these blood conditions are irresponsive to bacterial inoculation and call for appropriate chemical medication, in this case the administration of citric acid in 30-grain doses, repeated at intervals of three hours or longer.

Contraindications to Inoculation.—One of these, as already stated, is the condition of local and persistent induration marking the site of a previous inoculation. Again, it is desirable to postpone inoculations, especially for chronic affections, during the course of an intercurrent infection, and to avoid them as far as possible when the patient is fatigued or exhausted, or, in women, during menstruation. Alcoholic excess and probably the depressing effects of other drugs, like morphine, defeat the best effects of therapeutic inoculations, and bacterial injections should be avoided during or immediately after such intoxications.

CLINICAL APPLICATIONS OF OPSONIC THERAPY.—As has previously been mentioned, the infections, especially the localized ones, due to the pyogenic bacteria com-

prise the principal group of diseases suitable for opsonic therapy. It will scarcely be advisable, at this still comparatively early day in the development of therapeutic inoculation, to attempt a classification of these affections, which, as may be readily seen, can be based upon either anatomical or etiological grounds. A wiser course at this juncture seems to be to describe the various diseases somewhat in the order of the development of the practice, and, as a supplement to the general directions just given, to bring out the special points that experience has illuminated.

Acne.—This often stubborn and troublesome cutaneous affection belongs to Wright's first group of microbic diseases, viz., those "in which the bacterial process is strictly localized or shut off from lymph or blood circulation. In this class the opsonic index is persistently low, owing to the absence of immunizing stimuli." A fact of greater importance is that artificial inoculations with the predominating and probably causative microbe of acne, a staphylococcus, usually the albus, occasionally the citreus, or albus and citreus mixed, are generally beneficial from the therapeutic standpoint, even in cases where other measures have failed after long trial.

Not all cases of chronic acne, however, give a curative response under attempted therapeutic immunization with the causative microbe. The particularly suitable ones belong to the type of acne vulgaris, in which pustules and sluggish indurations abound. Mixed forms with a tendency to the rosacea type are obstinate at times, or may even refuse to be influenced. Again, some of the most persistent cases seem to be in that passive state which may be met in other severe or long-standing infections, where satisfactory immunizing responses cannot be evoked; and where, presumably, the capacity for a curative impetus on the part of the mechanism of immunization has been worn out by the repeated efforts at spontaneous or artificial auto-inoculation. In general terms it may be stated that a satisfactory issue is possible in proportion as the disease is recent, and this proposition applies to other morbid conditions amenable to therapeutic bacterial inoculations; though many times the opsonist will be gratified to observe an old and stubborn acne, resistant to patient trial of all the measures adopted by skilled dermatologists, mend with pleasing rapidity under the influence of bacterial inoculations.

With the uniformity of a staphylococcic infection as an etiological factor of acne in mind, it has been proposed that this disease is of a class particularly suited to the use of extraneous or "stock" vaccines, of which a mixture of the albus and citreus is advised. But to one who has worked extensively on the bacteriology of acne, and has familiarized himself with the variations presented by different "strains" of even so common an organism as *Staphylococcus albus*, and particularly if, as is commonly the result in prolonged experience with this disease, he finds that at best only temporary beneficial effects are secured by such stock vaccines, the advisability of employing vaccines from staphylococci of autogenous origin will impress itself. To the writer's mind, even in so comparatively simple a pyogenic disease as acne vulgaris, there seems to be a peculiar and special merit in the autogenous microbe, speedily isolated and reintroduced with as little artificial manipulation as possible; and the preference expressed by an intelligent patient for a vaccine of his own organism becomes more than a fanciful whim in the face of the possibility of obtaining a microbe from individuals with latent and subsequently developing syphilis, as has happened at least twice in my experience.

Inoculations against acne are performed with doses of 100 million to 500 million staphylococci, and at intervals of about five to ten days, depending on the course of the immunity wave as shown by the staphylo-opsonic index, or by the clinical manifestations. These inoculations usually produce a symptomatic negative phase, some soreness in the injection site, or even slight inflammatory reaction, chilliness, depression, slight anorexia,

together with aggravation of the pimples. A sense of well-being and an improvement in the cutaneous lesions follow in the positive phase, while the second negative phase is usually accompanied by a fresh outbreak of pustules, generally much smaller and more superficial than in the untreated state, and giving plain indication for another inoculation. The duration of treatment varies considerably. Some aggravations and long-standing cases of acne have been brought to perfect recovery after three to five inoculations; others require much more prolonged treatment, and even where failure to arouse an immunizing response does not occur there are cases in which a long course of inoculations effects no more than a marked improvement.

Staphylococcic Sycosis.—As an aid when established methods of treating non-parasitic sycosis barbæ fail, inoculations with the autogenous staphylococcus (usually aureus) promise to be signally beneficial as attested by a number of chronic and obstinate cases of this disease which have been brought to full recovery; the inoculations, spaced and in dosage like those for other localized cutaneous infections, generally making superfluous the more heroic measures like epilation; though, at times it will be found desirable to fortify the inoculation with x-ray epilation.

Furunculosis.—Subacute and chronic boils are successfully combated by inoculations of *Staphylococcus aureus*, a fact which Wright demonstrated in his early attempts at bacterial therapy. Here one may use stock vaccine, though for reasons already alluded to, and again because some cases of chronic boils react more favorably to autogenous vaccines, the latter are preferable. Opsonic measurements show a characteristic immunity wave, and where the opsonic index is used for guidance inoculations are performed at intervals of five to seven days, and in doses of 100 to 500 million staphylococci. Very often a single inoculation is sufficient to bring an end to the recurrent furunculosis; again, one must repeat the injection according to symptomatic indication, chief among which is a tendency to relapse.

Both in acne and in furunculosis the usual surgical measures, like deep incision and forcible expression of comedones or pus, are superfluous when inoculations succeed in modifying the disease.

Staphylococcic Carbuncle.—As in acute and chronic boils, so in this closely allied but more formidable infection with its necrotic tendency, inoculations with autogenous staphylococci, if performed early, abort the carbuncle; and at later stages hasten the reparative process, even in the more chronic and sluggish types.

Eczema.—That some forms of eczema will be benefited by, or even yield completely to, bacterial inoculation seems to be promised by the author's experience. In several cases of chronic localized eczema *Staphylococcus citreus* or *aureus*, sometimes alone, again mixed with *albus*, have been readily recovered from the eczematous lesions, and under the influence of these staphylococcal inoculations in average doses of 200 million, spaced five to seven days apart, improvement and recovery have been effected in individuals whose malady had been treated by various other methods without avail.

Of course this is not to say that ordinary acute eczema should be subjected to bacterial therapy, or at least not until the generally successful local applications have failed to promote recovery. But in the more chronic and intractable eczemas, and probably also in the generalized eczema of infancy where the usual lines of treatment are ineffective, inoculations with autogenous staphylococci are worthy of trial, alone or in combination with other well-established measures.

Impetigo.—This cutaneous disease usually subsides under the local and general measures in vogue with dermatologists, but occasionally a case is encountered in which the pustular lesions of impetigo fail to mend, and continue to appear in spite of these efforts. It is here in order to test the efficacy of inoculations with staphylococci which may alone be isolated from the impetiginous pus, or of the staphylococcus and streptococcus

when these are associated, and, if the writer's personal experience is a criterion, very satisfactory results are thus obtainable.

Seborrhæic Eczema.—In two cases of this generally chronic affection, which is often confused with psoriasis, but differs in both its morbid anatomy and its bacteriology, I have achieved a successful outcome by inoculations of the *Staphylococcus aureus* secured from the diseased skin, in doses of 200 to 500 million, at intervals of five to fourteen days; and this after thorough trial of the measures practised by skilled dermatologists.

Psoriasis.—Likewise in psoriasis I have obtained undoubted evidence to indicate that valuable aid in this too often intractable disease will be afforded by inoculations of the *Staphylococcus albus*, which is readily obtained in culture from the psoriatic scales; although this is not to claim that such staphylococci are the sole etiological factors, if, indeed, they have any causative relationship. Here relatively large doses of staphylococcus (500 million to 1 billion) seem to be required, especially in treating generalized psoriasis of long standing, and the aid of such measures as hot baths, friction, and massage to increase the blood supply to the superficial layers of diseased skin is desirable.

Traumatic Surgical Infection.—A very wide field for the useful application of opsonic therapy is embraced in the infections that follow accidents or surgical operations. Here, of course, we usually have to do with the common pus microbes, and in such affections as phlegmon, cellulitis, lymphangitis, and lymphadenitis produced by the staphylococci and streptococci, therapeutic inoculations, in conjunction with the less severe surgical measures like hot fomentations, induced hyperæmia, and incision limited in extent and only for the purpose of evacuating and allowing gravity drainage for pus, will be of signal service. In the more acute and more rapidly spreading infections inoculations are best performed at intervals of one to three days until the process is in check, after which the interval is to be extended according to symptomatic indications.

Sinuses and Fistulas.—Unhealed, discharging tracts following operation or the spontaneous discharge of purulent accumulations which have stubbornly resisted all the artifices of the surgeon, can, in practically all instances, be benefited by inoculations of one or more bacterial species secured from the discharge, or from the diseased tissue of the tract; and in the majority of cases the reparative impulse can be maintained by further bacterial therapy until full healing has occurred; provided, of course, that there is no mechanical obstacle to final success, like necrotic bone, or foreign material accidentally lost during surgical manipulations. In the more recent unhealing openings, where the bacteriology is usually that of a single well-known species like one of the staphylococci, streptococci, or colon bacillus, one or two inoculations may suffice to turn the tide in favor of rapid and perfect healing. In more chronic sinuses, especially if multiple, and harboring several bacterial species in the pus, inoculations must naturally be longer continued, and modified to meet such changes as the flora of the discharge may show. But even in very ancient examples of single and multiple fistulas or sinuses, perhaps even of a mixed tuberculous and pyogenic origin, or fecal in character if in the abdomen, successful closure can at times be achieved by appropriate bacterial inoculations, together with progressive betterment of the patient through the control of vicious auto-inoculation.

Septicæmia, Puerperal Sepsis, and Infective Endocarditis.—Contrary to the opinion expressed by Wright in his earlier communications, it now appears that, occasionally at least, a favorable issue is to be anticipated where bacterial inoculations are directed to the conquest of a generalized infection. The most striking case in this category is the one reported by Barr, Bell, and Douglas, in which a patient with streptococcus septicæmia, iliac venous thrombosis, a dilated heart with its usual consequences, and what was clinically diagnosed as an infective endocarditis, was brought to a final re-

covery with inoculations of the streptococcus secured from the blood. Several additional cases have been reported in which a streptococcus or staphylococcus septicæmia was treated by bacterial therapy. In some of these cases the presence of infective endocarditis was established clinically or by autopsy, and while the issue was not favorable in all these attempts, enough has been learned to justify the trial of autogenous therapeutic immunization in these desperate conditions.

My first attempt to treat a puerperal sepsis by inoculations was most satisfactory in its outcome, since two injections of the streptococcus obtained unmixed from the exudate of the infected endometrium served, in three days, to change the exceedingly grave aspects of what appeared to be a violent infection to a state of rapid and perfect convalescence.

Thoracic Empyema.—How much aid therapeutic immunization may be expected to give in recent empyemas, freshly drained by adequate opening, is problematical, for of course there is to be considered the spontaneous tendency toward healing in such cases, particularly in young individuals. A wise precaution under these circumstances would be to prepare and have in readiness a vaccine of the autogenous pneumococcus or streptococcus, most common inciters of recent empyemas, and to institute inoculations in case of tardy or unsatisfactory progress.

With old, neglected empyemas, and especially those with bronchial perforation, the outlook even with proper drainage and all manner of surgical manipulations is generally recognized as unpromising. Here the indication for therapeutic inoculations of the microbes, isolated from the pus obtained through the thoracic incision or by aspiration, may be said to be always in order, and, if carried out with proper precautions and in conjunction with adequate drainage, will materially improve the prospects for full recovery.

Finally in that group of much-dreaded examples of old, unhealed, suppurating empyemas, with or without bronchial perforation, where surgical interventions like incision, thoracoplastic operations, and all kinds of devices for obtaining continuous drainage fail, many apparently hopeless cases can be brought to final perfect restoration by correctly applied immunization with one or more microbial species of autogenous origin. It is, of course, essential to success for opsonic therapy to be instituted before extensive amyloid metamorphosis has hopelessly damaged the viscera, and that the individual should not have had his power of response destroyed by habitual use of alcohol or opium; and failure even in the absence of these contraindications should not be too heavily charged against the inoculation method. But with the capacity for immunizing impulse still in existence, some truly surprising results are in store for those who will patiently subject to treatment these old thoracic suppurations, with inoculations of the microbes constituting the flora of a chronic empyema (changing the vaccines as the bacteria of the flora may change). Such seemingly impossible effects as healing of a very old bronchial perforation, diminution and cessation of suppuration, and, by some means, the closure of immense pleural pus sacs from which for many months copious and not rarely most fetid pus has issued, are to be accomplished by the inoculations, aided only by general hygienic measures, and possibly by medication to increase the coagulability of the blood, which is usually low in these conditions.

Urinary Infection.—In one particular form of non-tuberculous ascending urinary infection the prospects for successful opsonic therapy seem good, judged by the cases already reported, of which the author has furnished one most striking record, viz., in that due to infection with the colon bacillus. Here, even in a condition that seemed desperate and hopeless judged by all ordinary standards, and where a heavy pyuria accompanied a cystitis and unilateral pyonephrosis, rapid recovery followed on five inoculations of the autogenous colon bacillus (which, because it happened to be much

less virulent than the type obtained in other abdominal suppurations, was used in doses of 200 million to 1 billion spaced five to ten days—a recovery that has been perfectly sustained for over a year since the treatment began.

But in other cases of cystitis, as those with stone or enlarged prostate, especially where a mixed bacterial flora abounds, the outlook is not so good, though one may at least relieve the patient by the agency of autogenous bacterial inoculations from such evidences of vicious auto-inoculation as the symptoms of chronic sepsis, and of rheumatoid affections, which here, as elsewhere with chronic suppurative foci, may cause much distress.

Other Localized Pyogenic Affections.—In contemplating the field of useful application for bacterial therapy as directed to localized non-tuberculous and non-gonorrhoeal suppurations, it is clear that a wide range of regional diseases is embraced. Among those that have already been attempted, and many with satisfactory outcome, there are to be mentioned *acute and chronic otitis media* and *mastoid suppuration*, *suppuration of the cranial sinuses with thrombo-phlebitis* and the *antrum of Highmore*, *pyorrhæa alveolaris*, and *abscesses of the salivary glands*. *Chronic bronchitis*, in some of its forms at least, is also amenable to therapeutic immunization as I have learned in one long-standing case of recurrent feetid bronchitis with *Bacillus mucosus capsulatus* as the predominating organism, and in which most satisfactory curative impulses have followed the inoculations with the autogenous bacterium. Colon bacillus infections of the *gall bladder* and of the *intestinal mucosa* have been successfully treated by inoculations; and my personal experience in one such case inclines me to believe that in *acute appendicitis*, when operation is refused, inoculation with colon bacilli from appendiceal pus will prove alike justifiable and beneficial.

Pneumonia and Acute Cerebrospinal Meningitis.—Some experiments with pneumococcus inoculations in pneumonia have been reported; their outcome was inconclusive, as might readily be imagined. Likewise, inoculations with the meningococcus in cerebrospinal meningitis have been tested in isolated cases, and here again no opinion is justifiable as to the results, for several cases were in the advanced hydrocephalic stage in which final recovery without treatment is not uncommon, and the proportion of satisfactory issues in the earlier cases was not such as to rule out the possibility of spontaneous recovery.

Regional Tuberculosis.—Inoculations of tubercle vaccine (T. R. or B. E.) have been employed with benefit in many forms of localized infections with the tubercle bacillus. In *lupus* of the skin a considerable number of cases have already been recorded, most of them failures under other modes of therapy, and of great chronicity; and in the majority full recovery has been achieved by inoculations of tubercle vaccine, varying in duration from one month to a year or even longer. In treating especially the dry, scaly, erythematous form of lupus, and also in connection with tuberculin inoculations for tuberculous adenitis, even when a mixed infection is not demonstrable, occasional injections of staphylococcus vaccine appear to improve the progress; this is also true of some other tuberculous diseases, as of the bones, joints, and synovial sheaths. In *lupus* of the mucous membranes, especially in the chronic ulcerative types, beneficial results usually follow the inoculations of T. R. alone, or in combination with pyogenic cocci.

Chronic tuberculous lymphadenitis marks another affection in which the application of Wright's method proves most advantageous. Improvement and ultimate recovery under the impulse of therapeutic immunization, with small doses of tuberculin (aided by vaccines of common pyogenic bacteria if these complicate the adenitis) is the rule in these cases, and much is to be accomplished in the way of avoiding the extensive operations of complete eradication, until recently the only rational therapeutic procedure. Of course the

opsonist will encounter cases in which liquefaction of tuberculous gland substance cannot be avoided, but, with the immunity aroused by proper inoculations, one may evacuate these accumulations through aspiration with a syringe, or by drainage through the track of incision with a long, narrow tenotome, thus avoiding even the scars of ordinary incisions. And where calcareous or dry caseous masses fail to resolve, they can be removed through small incisions. Where sinuses are present from previous operations or spontaneous evacuation, the search for secondary microbes should not be neglected. The duration of inoculation treatment directed against tuberculosis of the lymph glands varies. I have seen an old sinus close and the mass of enlarged cervical glands melt into impalpable tissue under the influence of three inoculations of T. R. and staphylococcus vaccine, spaced ten days apart. Another case with two sinuses and extensive unilateral cervical adenitis, with mixed tubercle bacillus, staphylococcus, and streptococcus infection, has made such progress that the upper sinus is healed, the lower one almost closed, and the mass of glands reduced to three with probable calcareous metamorphosis: this the result of three months of inoculation treatment, as contrasted with one year's unavailing effort with ordinary medical and operative measures. Again, this time, where the affected glands while large were originally very hard and probably caseous and calcareous, no appreciable diminution has been noted after three months of T. R. inoculations.

In *urinary infection* with the tubercle bacillus the outlook for therapeutic inoculation is also promising. My first patient, whose treatment began over a year ago and who then suffered with frequent urination, marked pyuria (tubercle bacillus and pneumococcus), debility, a cough, and signs of apical trouble in the left lung, and in whom a diagnosis of tuberculosis of the left kidney and bladder had been made, is to-day in a state of what seems to be perfect recovery, both as to general health and a urinary secretion absolutely free from pus and tubercle bacilli. In this case inoculations with T. R. and the pneumococcus from the urine were carried out steadily on alternate weeks for three or four months, then at longer intervals. Similarly favorable results have been reported by Wright and his associates.

Among the other regional tuberculous infections of hæmatogenous origin, those of *bones*, *joints*, *tendon sheaths*, *iris*, and of the *epididymis* have been reported upon as subjected to opsonic therapy. As a rule the results have been satisfying; improvement was observed in nearly all the patients remaining under treatment a sufficient period, and a goodly number of recoveries, some of them very remarkable, are specified. The duration of treatment varied from two or three months to a year or longer.

Pulmonary Tuberculosis.—It is still too early to speak with assurance as to the range of usefulness for opsonic therapy in tuberculosis of the lungs, or as to the results to be obtained by Wright's method of very minute doses at comparatively long intervals compared with the method of graduated intensive immunization with tuberculin as carried out by others. From several quarters favorable results have been reported, even in cases of well-advanced phthisis, especially in those in which vaccines of autogenous streptococcus or staphylococcus were used along with the tubercle vaccine. But here, as in any other promising line of biological therapy directed to this formidable malady, so many obstacles of a mechanical kind (caseous, calcareous, necrotic material, especially in cavities) are present in the affected lungs of advanced phthisis that neither success nor failure should be too greatly magnified. With early and sharply localized pulmonary tuberculosis, or even in more extensive disease in which the clinical picture of the non-febrile type is presented, bacterial inoculations appear to augment the reparative process, especially when used in conjunction with the hygienic treatment now so popular.

Gonorrhæal Affections.—Here, as with tuberculosis,

inoculations are usually performed with a "stock" vaccine, because of the difficulty frequently encountered in isolating and cultivating the gonococcus from a single case. Testimony as to the value of gonococcal inoculations is conflicting, and, in part at least, this may be due to the variation in therapeutic effectiveness of vaccines of varying origin. However, with a good gonococcus vaccine there is no question about its therapeutic potency when directed against the inflammatory complications of acute and subacute gonorrhœa, as the writer has seen most strikingly evidenced in cases of *epididymitis*, *balanoposthitis*, *proctitis*, and *conjunctivitis*. In acute gonorrhœal arthritis, also, the outcome following inoculations of a potent gonococcus vaccine in doses of 10 to 50 millions is gratifying. Many cases of chronic gonorrhœal arthritis, some, indeed, in which serious joint changes seem to prohibit improvement, do remarkably well under a course of gonococcus inoculations, especially when, in the common event of a secondary infection of the structures about the base of the male bladder, inoculations with the secondary organisms are used along with the gonococcus vaccine.

In the treatment of *acute gonorrhœal urethritis* the function of inoculations of the gonococcus is not yet clearly defined. In using this organism alone it is questionable whether the average case of blennorrhagia is beneficially affected by inoculation. However, it is here that we frequently have to deal with a mixed infection, and, as I have satisfied myself on a number of occasions, one not uncommon associate of the gonococcus is the pseudodiphtheria bacillus, with whose pathogenic activities we are only recently becoming familiar. In my own work it has appeared that the results in acute urethritis were much better when the mixed gonococcus and pseudodiphtheria vaccines were used in cases with the corresponding infections, but I have yet to satisfy myself that this affection or *chronic urethritis*, *vesiculitis*, or *prostatitis* can be conquered with inoculations unfortified by the other common remedial agents, though they promise to become most useful adjuncts. In something of the same bearing it is probable that therapeutic inoculations, as now practised, will stand in relation to the gonorrhœal diseases of women and of children.

Inoperable Malignant Tumors.—Considerable experimentation has been done in testing the efficacy of bacterial inoculations, specifically of the *Micrococcus neoformans* of Doyen, in inoperable malignant tumors. This is the microbe which Doyen found frequently present in carcinoma, and for which he wished to prove an etiological relationship. In both its morphological and biological features the organism resembles *Staphylococcus albus*, and it is not improbable that it really is a member of this common pus-forming group, which has penetrated into the cancerous tissue as a secondary invader, perhaps thus hastening the destructive growth of the neoplasm. It is on somewhat such an assumption as this that Wright has proposed the use of neoformans vaccine in treating inoperable tumors, and there are trustworthy reports that, in some cases at least, most surprising betterment has followed these inoculations, amounting, in a few fortunate instances, to a seemingly perfect recovery; an early report recording seven such favorable cases being that by Jacobs and Ceets.

In the only case of inoperable malignant tumor that I have personally undertaken to treat by bacterial therapy, a recurrent malignant adenoma, filling the pelvis with a large adherent mass, and penetrating the rectum, to produce ulceration, bleeding, difficult stools, and much pain, very decided diminution in the tumor mass, and a comforting amelioration of the rectal distress and pain, have been brought about by inoculation of *Micrococcus neoformans*, to which has been added a vaccine from the colon bacillus secured from the pus of the ulcerated rectum.

Albert P. Ohlmacher.

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The literature of opsonic therapy is still very recent, as is this promising method of practice. Until a year ago practically all

the articles on the subject appeared in the English medical periodicals (specifically *The British Medical Journal*, *Lancet*, *Practitioner*, and *Proceedings of the Royal Society*) during the preceding four years, and from the pen of Wright or his immediate associates. Wright's "A Short Treatise on Antityphoid Inoculations" contains full reference to the papers which had appeared up to the time of its publication (1904). Later articles can be found by consulting the indices of the periodicals just mentioned, and by following the current issues of these journals.

During the last year articles dealing with both the theoretical and the practical aspects of opsonic therapy have appeared in such American journals as *The Journal of the American Medical Association*, *The Journal of the Ohio State Medical Association*, *The American Journal of the Medical Sciences*, and *Surgery, Gynecology, and Obstetrics*; while the more distinctly theoretical aspects have been discussed in such special periodicals as *The Journal of Experimental Medicine*, *The Journal of Medical Research*, and *The Journal of Infectious Diseases*.

In the German literature the principal articles are those by Weinstein in *Berliner klinische Wochenschrift*, Nos. 30 and 39, 1906.

PERITONITIS.—(Peritonæitis, Inflammatio peritonei.) The peritoneum is a thin membrane of connective tissue extremely rich in blood-vessels and lymphatics, and is covered by a single layer of flattened endothelial (mesothelial) cells (often called epithelial). These cells are chiefly polygonal, but the cell outlines are often very irregular, serrate, or wavy. By treatment with silver nitrate or by *intra vitam* staining with methylene blue, the cement lines between the cells can be made out; and by especial methods of technique the so-called intercellular protoplasmic bridges connecting the cells may be demonstrated. The connective-tissue layer consists of an interlacing network of fibrous connective-tissue bundles, numerous elastic fibres, and connective-tissue cells. Through this there runs a very abundant capillary and lymphatic network having a free anastomosis. The majority of writers hold that the lymphatics communicate directly with the peritoneal cavity by means of small openings between the mesothelial cells, known as stomata. Some of these writers regard the endothelial lining of the lymph spaces of the peritoneal basement membrane as continuous with the lining of the peritoneal cavity. This is not the case, however, and the mesothelial cells form a probably unbroken layer over both the blood and the lymphatic vessels, the processes of absorption and secretion being carried on through the two layers of cells, endothelial and mesothelial. The absorption capacity of the peritoneal surface is very great, being fully equal, in the case of experiments with certain poisons, to that of direct intravenous injections. Gases, fluids, and even morphological elements may be quickly removed from the peritoneal cavity. On the other hand, the secretory activity of the immense vascular surface of the peritoneum is very great, and in disturbances of the vascular secretion an immense amount of exudate may pass through the peritoneum into the peritoneal cavity. The endothelial and connective-tissue cells of the basement membrane respond very quickly to "irritation" of any kind, and fibroblastic activity is set up more quickly in the peritoneum than anywhere else in the body. The course of peritoneal inflammations is considerably modified by these factors.

The peritoneum lines the entire abdominal cavity, and is reflected over the organs contained within it. Over the organs it forms the serous coat or capsule (*tunica serosa*). The membrane is attached to the underlying parts by a subserous coat of adipose tissue, connective-tissue bands and elastic fibres. Over the organs the subserosa is but slightly developed. The anatomical relations of the peritoneum to the abdominal wall, its investiture of the abdominal organs, the intimate relations of the peritoneal cavity to the female genital tract, etc., in connection with its very vascular structure, peculiarly predispose this membrane to the occurrence of inflammatory processes. Such a predisposition is shown by the fact that peritonitis is one of the most common and important clinical conditions. It is also one of the most serious. The high mortality of acute general peritonitis makes it one of the most dreaded affections. Even in these days of aseptic surgery when so many operative procedures have been divested of their chief dangers, peritonitis still remains to the abdominal sur-

geon and gynecologist one of the complications most feared and most carefully to be avoided.

The occurrence of peritonitis is not dependent upon climatic, seasonal, or meteorological influences. Females are more frequently affected than males, this fact being dependent upon the important rôle which diseases of the female genital tract play in the causation of peritonitis. It is therefore seen more often during the years of sexual activity, but may occur at any age. It is of not infrequent occurrence in young children. The relation of peritonitis as a complication to many of the acute infections makes its occurrence to a certain degree associated with epidemics of these diseases. Alcohol is regarded as a predisposing factor.

ETIOLOGY.—Peritonitis may be *primary* or *secondary*.

Primary peritonitis is, if we except the surgical form, of much more rare occurrence than the secondary. It is usually *traumatic*, more rarely, *idiopathic*, *spontaneous*, or *rheumatic*.

Traumatic peritonitis is most commonly due to perforating wounds of the abdomen. Abdominal injuries in which the wall is not penetrated rarely, if ever, directly cause peritonitis. Nevertheless, blows, kicks, falls, etc., are often adduced as causes of peritonitis. The more severe the injury, the more likely is the occurrence of peritonitis. Hemorrhage into the peritoneal cavity is usually followed by inflammation of the peritoneum. Likewise, trauma may indirectly cause peritonitis through the perforation, laceration, tearing, or bruising of the stomach or intestines, rupture of the gall bladder, pancreatic duct, urinary bladder, etc., these lesions permitting the entrance of micro-organisms into the peritoneal cavity. The perforation of the œsophagus or stomach by the careless passage of a sound or stomach tube may also be a causal factor in the production of peritonitis.

Operative or *surgical* peritonitis may be mentioned in this connection. Before the days of antiseptics and asepsis a large proportion of laparotomies were fatal from the peritonitis following the operation. Even at the present day the chief anxiety attending operations involving the peritoneal cavity is the possibility of peritonitis. The vast improvement in surgical technique has, however, greatly reduced the number of cases of post-operative peritonitis, and in certain operations in which there is, with proper methods, no opportunity for infection the peritoneal cavity is opened with a certain degree of impunity. The occurrence of surgical peritonitis is dependent upon several factors: the character of the operation and the possibility of infection during the operative procedures, the amount of damage done to the peritoneal tissues, the state of the general resistance of the membrane to infection, etc. Surgical peritonitis is due to the introduction of bacteria into the peritoneal cavity. But not all bacteria which gain an entrance into the peritoneal cavity set up an inflammation there. It has been shown experimentally that rather large quantities of bacteria, even of the pus cocci, may be introduced into the peritoneal cavity of animals without causing peritonitis, the bacteria entirely disappearing after a short time. The presence of a tissue lesion, even though very slight, or the simultaneous introduction into the cavity of irritating substances, furnishes the conditions requisite for the growth of the bacteria and for the production of an inflammation. The peritoneum therefore when uninjured must possess a certain protective power against bacteria. This resistance is found to be lowered in the case of hemorrhage into the cavity, after the removal of ascitic fluid, and in cases of pseudomyxoma peritonei. The general condition of the body, conditions of intoxication, cachexia, etc., also play a rôle of importance. Fatal peritonitis may follow the tapping of the abdomen in ascites, the small number of bacteria introduced by means of a septic trocar being sufficient to overcome the lessened resistance. When modern methods of asepsis are properly carried out the dangers of surgical peritonitis are relatively slight in all cases in which the contamination of the peritoneum with septic material can be avoided. Even when this contamination does occur,

the modern procedures of thorough irrigation have greatly reduced the chances of infection.

The existence of a *peritonitis rheumatica (refrigeratoria)* has been denied by many writers. While the effects of cold as a factor in the etiology of peritonitis were formerly greatly exaggerated, there can be no doubt, from the large number of observations made by reputable clinicians, that attacks of peritonitis may follow the sudden chilling of the overheated body, prolonged exposure to cold or wet, lying upon the cold damp ground, etc. The effects of such chilling of the body are especially noticeable when the abdominal vessels are overfilled with blood (*physiological congestion*). In women, particularly in girls at the time of puberty, a wetting or chilling of the body at the menstrual period is not infrequently followed by peritonitis. In all of these cases the effect of the refrigeration is not directly to excite the peritonitis, but to render the membrane less resistant to infection. The chilling plays the same rôle here as in the case of the mucous membranes. Diplococci have been demonstrated in the exudate of cases of so-called rheumatic peritonitis; and it is very probable that all such cases are infections following and dependent upon a lessened resistance of the body.

Cases of *idiopathic* or *spontaneous* peritonitis have also been reported clinically.

The autopsy findings in such cases show the presence of an infection proceeding from the female genital tract, the appendix, or some other of the abdominal organs. Such cases occur most frequently in females and in very young persons. In the former the infection is nearly always secondary to some unsuspected condition of the internal genitals. The gonococcus plays an important rôle in such cases, particularly in very young girls. It has been said that the peritonitis apparently arising spontaneously in young girls is usually gonococcal, a gonorrhœal infection of the genital passages existing at the same time. In young male children cases of apparent spontaneous peritonitis are usually found to be due to appendicitis. Further, spontaneous cases of peritonitis have been found at autopsy to be ambulatory typhoid, acute tuberculosis of the peritoneum, etc. On the whole it may be said that the existence of a true idiopathic peritonitis, while probable, has not yet been definitely demonstrated. A *cryptogenic hematogenous* infection of the peritoneum is of course possible and certainly occurs in tuberculous peritonitis, but has not yet been shown positively to occur in the case of the pyogenic organisms.

Likewise the existence of a toxic peritonitis, though assumed by some writers, has not been demonstrated. The occurrence of so-called *nephritic* or *uræmic* peritonitis seen in the late stages of Bright's disease is to be regarded as of the nature of a terminal infection, and similar to the pericarditis and pleuritis occurring in the same disease. The occurrence of peritonitis in association with or following various forms of intoxication is to be explained in the same way as the rheumatic—the lessened resistance of the body tissues and the pathological alterations of the body juices predispose to infection.

Since primary inflammations of the pericardium and pleura are of relatively more frequent occurrence, the greater rarity of primary peritonitis may be explained by the assumption that the peritoneum possesses a greater resistance and protective power than the other serous membranes. This relative greater immunity of the peritoneal cavity has been demonstrated experimentally.

SECONDARY PERITONITIS.—It should be noted at this point that various writers upon the subject of peritonitis are not agreed in their conceptions of primary and secondary peritonitis. In a very broad sense the term primary may be applied to those forms of peritonitis which are not secondary to, or do not occur in association with, any other acute or chronic disease, hence not metastatic; and, further, which do not arise by contiguity from any of the organs or structures covered by the peritoneum. Terminal infections should then be classed as secondary rather than as primary. A number of recent

writers, notably Flexner, in retaining the old classification of primary and secondary peritonitis, make a much narrower application of the term *secondary* as applying to peritonitis. According to Flexner, by *secondary* peritonitis we should understand those conditions which follow operations upon the peritoneum or the contiguous viscera, and those in which the abdominal cavity becomes inflamed through the mediation of disease-contained viscera. By *primary* peritonitis should be understood an inflammation, usually diffuse, of the serous cavity, occurring without the mediation of any of the contained organs and independently of any surgical operation upon these parts. Such a primary peritonitis may arise as an independent affection or develop in the course of infectious diseases in distant parts of the body. The micro-organisms causing the inflammation may be brought by the blood or lymph current or may pass through the intact intestinal wall. Flexner would therefore class as primary not only the terminal infections of the peritoneum occurring in the course of chronic diseases, but also those forms of metastatic peritonitis in which the micro-organisms come through the blood or lymph without the mediation of some diseased organ or part. The reason given for this more arbitrary and narrower use of the term secondary and the wider application of the term primary is that pathogenic micro-organisms may reach the healthy peritoneum without setting up an inflammation, but that "only an already inflamed peritoneum can be excited to peritonitis through the agency of pathogenic micro-organisms." Used in this way the terms primary and secondary indicate the character of the affection rather than the source of the cause or the manner in which the peritonitis arises. Since such a usage may be confusing, the writer has preferred to adhere to the more commonly accepted use of the terms as given above, viz., *primary peritonitis*, an inflammation of the peritoneum arising primarily and independently of other processes, as the result of chemical or mechanical irritation or as a direct or cryptogenic infection, or as the result of a lessened resistance of the peritoneum due to trauma, toxic conditions, or altered conditions of the peritoneum caused by foreign bodies, presence of fluid, etc., analogous to primary infections in other parts of the body; *secondary peritonitis*, an inflammation of the peritoneum, secondary to some other process, arising by contiguity or metastasis, or occurring as a terminal infection. Even with this broader standard of classification no hard-and-fast lines can be drawn. Inasmuch as cases of primary peritonitis are rare, and as the peritoneum possesses a normal resistance against pathogenic micro-organisms, practically all cases of peritonitis are secondary.

In the great majority of cases secondary peritonitis arises through an *extension* of an inflammatory process from some contiguous viscus or part. There is no organ or tissue in direct contact with the peritoneum from which such an extension may not occur. The possibilities are so numerous that it is necessary to refer here only to the most common or important. The extension to the peritoneum may or may not be accompanied by perforation into the peritoneal cavity. In the latter case the resulting inflammation is known as a perforative peritonitis.

Perforative Peritonitis.—This is the most common form of secondary peritonitis. It may result from the perforation into the peritoneal cavity of an infected wound of the abdominal wall or of a viscus (traumatic or operative), or from the perforation, as the result of inflammatory processes, of the wall of the stomach, intestine, gall bladder, pancreatic duct, urinary bladder, uterus, tubes, blood-vessels, lymph vessels, etc. Abscesses of the abdominal viscera, echinococcus cysts, tumors, burrowing suppurative processes in the retroperitoneal tissues, etc., may also give rise to perforative peritonitis. It is hardly expedient to enumerate here all the possibilities whereby a perforative peritonitis may arise, and only those of greatest clinical importance will be mentioned.

In the case of the *stomach* perforative peritonitis may be caused by carcinoma, gastric ulcer, abscess, phleg-

monous gastritis, action of corrosives, foreign bodies, etc. In the *intestines* ulcers (typhoid, dysenteric, catarrhal, tuberculous, syphilitic, carcinomatous, etc.), new growths, foreign bodies, parasites, gall stones, fecal concretions, fecal obstruction, intussusception, ileus, hernial incarceration, etc., may lead to perforative peritonitis. Perforation of a suppurating *appendix* is one of the most common causes of peritonitis.

In the case of the *spleen* perforative peritonitis may be caused by splenic infarcts, abscesses, echinococcus cysts, acute splenic tumor leading to rupture of the organ, rupture of a dilated splenic vein, metastatic tumors, etc. In the *liver* the same condition may result from abscesses, echinococcus cysts, rupture of bile passages, biliary concretions, new growths, etc. Rupture of the *gall bladder* or *common duct*, ulcerative processes in the walls of the gall bladder or ducts, presence in these of concretions, etc., may likewise lead to perforative peritonitis. This may be caused also by pancreatic concretions, abscesses and tumors of the *pancreas*, hemorrhagic and purulent pancreatitis, etc. Fat necrosis may or may not be associated with the peritonitis dependent upon pancreatic conditions.

Perforative peritonitis may also arise in connection with abscesses and tumors of the *kidneys* or *adrenals*, kidney tubercles, echinococcus cysts, renal calculi, purulent pyelitis, peri- and paranephritic abscesses, etc. Ulcerative and phlegmonous processes of the *urinary bladder*, new growths of the bladder, cancer of the *uterus*, purulent and gangrenous conditions of the uterine wall, purulent salpingitis, tubal pregnancy, tubo-ovarian abscess, ovarian tumors, rupture of Graafian follicle and ovarian cysts, suppurative processes of the retroperitoneal and mesenteric lymph glands, thrombophlebitis, and thrombo-arteritis of the abdominal vessels, rupture of abdominal aneurisms, rupture of the thoracic duct or dilated lymphatics, subperitoneal tumors and abscesses, psoas abscess, carious and purulent processes in the spinal column and pelvic bones, etc., may all lead to perforative peritonitis. In rare cases purulent processes proceeding from the mediastinum, pleura, pericardium, lungs, diaphragm, thoracic vertebrae, etc., may rupture into the peritoneal cavity and there excite an inflammation.

In the case of perforative peritonitis there will be found in the peritoneal cavity, in addition to the inflammatory exudate, various substances of very different nature according to the location of the perforation and the character of the contents of the cavity communicating with the peritoneal sac. Stomach contents, feces, fecal concretions, bile, biliary concretions, pancreatic juice, urine, urinary calculi, foreign bodies, parasites, blood, chyle, mucin, pseudomucin, colloid, etc., may be mixed with the exudate. According to the character and amount of the substances thus entering the cavity, and according to the character and amount of the peritoneal exudate the appearances seen at operation or autopsy will differ greatly.

Some writers distinguish a *secondary perforative peritonitis*, grouping under this head those conditions in which the exudate of a purulent peritonitis, originally not perforative, gains entrance to some neighboring organ, and through it finds an exit, as, for example, through the stomach, intestine, pleura, abdominal wall, etc. Such cases should more properly be styled *perforating peritonitis*.

Peritonitis Arising by Contiguity.—Peritonitis may arise secondarily by the direct extension of inflammation caused primarily by wounds (operative or traumatic) of the abdominal or pelvic wall, gastric ulcer, gastric cancer, phlegmonous gastritis, toxic gastritis, duodenal ulcer, intestinal ulceration (typhoid, dysenteric, catarrhal, tuberculous, syphilitic, carcinomatous), new growths of the intestine, coprostasis, intussusception, ileus, hernial incarceration, presence of intestinal concretions, parasites and foreign bodies, typhilitis, appendicitis, proctitis, liver abscess, new growths of liver, hepatitis, angiocholitis, inflammatory processes due to echinococcus, biliary

concretions, etc., pancreatitis, pancreatic abscesses and presence of pancreatic concretions, splenic abscess and infarction, hydatid disease of spleen, kidney abscess, peri- and paraneuritic abscesses, inflammatory processes caused by renal calculi, pyelitis, ureteritis, cystitis, inflammations of ovary, tubes, uterus, vagina, prostate, retroperitoneal or mesenteric glands, psoas abscess, congestive abscesses of spinal column or pelvic bones, inflammations of abdominal or pelvic vessels, suppurating buboes in the inguinal region, inflammatory processes of the mediastinum, cesophagus, pleura, pericardium and diaphragm, etc. In the case of inflammatory processes in the pleural cavity (tuberculous, empyema, etc.) the peritoneum is not infrequently involved, inasmuch as the lymph vessels of the diaphragm form a direct connection between the pleural and peritoneal cavities.

Next to the gastro-intestinal tract the *female genital tract* is the most frequent source of peritoneal infection. In women genital peritonitis is by far the most common form of the affection. During the puerperium or as the result of attempts at abortion, operative procedures, intra-uterine injections, etc., the genital tract may be directly infected; less frequently the infection occurs at other times, as for instance at the menstrual period. The resulting endometritis, metritis, parametritis or salpingitis may extend to the peritoneum and excite peritonitis. Purulent processes of the endometrium may extend directly up the Fallopian tubes. In other cases the extension of purulent processes from the vagina or uterus may take place through the lymphatics or blood-vessels. Large abscesses of the uterine wall or tube may break directly into the peritoneal cavity. Further, cases of apparently primary peritonitis have been reported as occurring in pregnancy without any association with rupture of the uterus or other complications of pregnancy. The discovery at autopsy of the existence of extensive renal changes makes it probable that such cases of peritonitis are secondary to the nephritis.

Gonorrhœa of the female genital tract is also an important factor in the production of peritonitis (see below). It must be noted further that in many cases of septic puerperal peritonitis the uterus and tubes serve as avenues of entrance to the agents of infection while remaining themselves in a normal condition.

An especial factor in the production of peritonitis of the female genital tract is that offered by the twisting of the pedicles of ovarian cystomata or of subserous uterine myofibromata. As a result of the shutting off of the circulation from the tumor, the tissues of the latter undergo necrosis, and the necrotic material offers a most favorable field for infection, particularly from the intestine. Such infections are very likely to result in a gangrenous peritonitis. In case infection of the dead tumor tissue does not occur a non-infectious peritonitis may result, the dead tumor acting as an irritating foreign body. A very virulent peritonitis may be thus excited, the exudate as well as the necrotic tumor containing no micro-organisms. Dermoid cysts appear to be especially susceptible to infection after twisting of their pedicles.

The rupture of an uninfected ovarian cystoma and the discharge of a thin serous fluid into the peritoneal cavity rarely excite a peritonitis, the fluid being quickly absorbed. The absorption power of the peritoneum under such circumstances is very great. Only those cystomata containing a firm jelly-like substance (mucin, pseudomucin, colloid) are dangerous, since the cyst contents cannot be easily absorbed and act upon the peritoneum as foreign bodies, leading to an organization and vascularization of the material (aseptic peritonitis, pseudomyxoma peritonei). It should be remembered, however, that in such cases secondary peritonitis is very likely to occur owing to the diminished resistance of the peritoneum; consequently a combination of pseudomyxoma and an acute or subacute peritonitis is not infrequent. Operation with the removal of the jelly-like cyst contents from the peritoneal surface after organization has begun is especially likely to be followed by infection of the raw surface thus exposed. In the case of the rupture of

cysts containing chemically irritating material (*pancreatic cysts, chyle cysts*), a non-infectious, acute, and very virulent peritonitis may be set up.

Secondary peritonitis is also not infrequently associated with metastatic carcinoma (*peritonitis carcinomatosa*) and tuberculosis of the peritoneum (*peritonitis tuberculosa*). These conditions will be discussed below.

In the *acute infections* peritonitis is occasionally met with as a complication. In *septicæmia* and *pyæmia* peritonitis is a very frequent complication. It occurs less often in *pneumonia, smallpox, varicella, measles, scarlet fever, diphtheria, erysipelas, malaria, relapsing fever, etc.* From the increasing number of cases reported *pneumonia* seems to be somewhat particularly associated with peritonitis, and the pneumococcus has recently been found in the peritoneal exudate of a number of cases. The peritonitis may be secondary to the pulmonary symptoms or may appear to be the primary condition, the peritonitis manifesting itself before the pulmonary affection. It is probable that such cases represent a general infection by the pneumococcus, the localization varying in different cases. They may therefore be classed as *peritonitic pneumonia*, in analogy to the types known as cerebral and gastric. Pneumococcal peritonitis may also be secondary to pneumococcal pericarditis, empyema, and arthritis. The occurrence in various parts of the body of multiple metastatic abscesses containing pneumococci is evidence of the pyæmic nature of the process.

According to Bednar peritonitis may develop after *vaccination*.

Metastatic peritonitis occurs in *malignant endocarditis* and in *pyæmia*. The primary focus may occur in any part of the body, and may be of very slight extent. Peritonitis has followed the infection of a circumcision wound, and very slight lesions in other parts of the body have led to the same fatal termination. It is not uncommon in such cases to find all the serous membranes involved—an acute panserositis; meningitis, pleuritis, pericarditis, and arthritis as well as peritonitis. Peritonitis may also develop during the course of *acute articular rheumatism*. The exact relation of the two conditions is unknown; the peritoneal inflammation is either metastatic or dependent upon a lessened resistance of the membrane to cryptogenic infections. Likewise acute peritonitis is sometimes associated with *acute nephritis*. It is possible that in these cases the intoxication plays some part in the development of the process, most probably by lowering the resistance of the membrane. The exudate in these cases is usually serous, and bacteria cannot always be obtained from it by culture methods; hence some writers regard these forms of peritonitis as of chemical origin and primary.

Terminal Peritonitis.—Peritonitis also occurs not infrequently as a terminal infection in chronic valvular disease, arteriosclerosis, chronic nephritis, cirrhosis of the liver, amyloid disease, tumor cachexia, scorbutus, etc. The peritoneum alone of the serous membranes may be affected, or the pericardium and the pleura may also become inflamed. Micro-organisms are usually present in the exudate. In those cases in which they are not found it is possible that they were present earlier in the disease, and later disappeared. It is of course possible that the peritonitis in some of these cases may be toxic or chemical, but it is more likely that the general intoxication has lowered the resistance of the membrane and cryptogenic infection has occurred.

There is also a close relationship between *syphilis* and peritonitis. Acute peritonitis not infrequently develops in the early stages of acquired syphilis, but is usually a secondary infection. It is not known whether an actual syphilitic peritonitis exists, though it is very probable that it does, inasmuch as a so-called idiopathic peritonitis is of common occurrence in syphilitic new-born. In the tertiary stage of acquired syphilis evidences of local peritonitis are common enough at autopsy. Chronic peritonitis and chronic perisplinitis are more common in syphilis than in non-syphilitics.

Foreign bodies (concretions, parasites, forceps, needles,

hairs, etc.) when aseptic produce a local encapsulating peritonitis. When septic they may excite a diffuse purulent or fibrinous process. Free bodies, such as fat tissue, blood clots, pieces of fibroid tumors, etc., may become calcified or encapsulated, setting up a local adhesive peritonitis. In *extra-uterine pregnancy* hemorrhage into the peritoneal cavity following the rupture of the sac may excite an intense peritoneal irritation even in the absence of infection. In such cases the blood itself must exert a chemical irritation upon the peritoneum, or irritating toxins are contained or developed within it.

Finally, during *intra-uterine injections* irritating substances may be forced through the tubes into the peritoneal cavity and excite a toxic inflammation. Such cases may occasionally be properly classed with the primary forms of peritonitis, but inasmuch as some inflammatory condition of the uterus or tubes is usually present it becomes difficult to say to what extent the infection is alone responsible for the peritonitis.

Parasites.—A number of observers have noted at autopsy the presence, in the peritoneal cavity, of intestinal worms in association with a perforative peritonitis. In some cases the perforation has been regarded as caused by the parasite (usually the common round worm), the peritonitis following the perforation. Some of the reported cases are very doubtful. Katsurado several years ago reported two cases of purulent peritonitis which he regarded as caused by round worms. A very careful examination, both at the time of operation and at the autopsy, failed to reveal any other cause for the peritonitis. In both cases the affection ran a very severe course. Osler and other recent writers accept the view that *Ascaris lumbricoides* may penetrate the intestinal wall and excite peritonitis. The *Amœba coli* has been found in the exudate of peritonitis.

Under rare conditions peritonitis may follow other conditions not mentioned above. As stated before it is hardly feasible to enumerate all the possibilities, but the most common and important sources of secondary peritonitis have been given; and if the extensive anatomical relations of the membrane are borne in mind it will usually not be difficult to trace to its source any secondary peritonitis that may be encountered.

BACTERIOLOGY.—Inasmuch as the great majority of cases of peritonitis are caused by bacteria the bacteriology of peritonitis becomes a matter of very great importance. In recent years a number of important investigations have been carried out along this line, but much work yet remains to be done before we shall possess a fully satisfactory knowledge of the subject. It has been demonstrated that very different forms of bacteria may be found in the exudate of peritonitis. In the majority of cases there is a mixed infection, several varieties of pathogenic bacteria being present, or a number of varieties of pathogenic and non-pathogenic bacteria may be found together. According to Tavel and Lanz the hæmatogenous cases of peritonitis are mono-infections, while those arising by contiguity from a neighboring diseased organ are usually poly-infections. It is probable that in some at least of the cases of mono-infection the single variety found may have crowded out other varieties which were originally present. This is particularly likely to have been the case in those instances in which the only micro-organism present is a harmless saprophyte. In those cases in which the exudate is sterile there is also the possibility that the original pathogenic bacteria causing the inflammation have died out.

The pathogenic bacteria most frequently found in peritonitis are the *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus albus*, *Bacterium coli commune*, *Diplococcus pneumoniae*, *Bacillus pyocyaneus*, and the *Gonococcus*. (Tuberculosis of the peritoneum will be considered separately.) Less frequently found are the *Bacillus typhosus*, *Bacillus aerogenes capsulatus*, *Bacillus proteus*, *Bacillus lactis aerogenes*, *Micrococcus tetragenus*, and a number of unidentified pathogenic and non-pathogenic bacteria.

In perforative peritonitis the *Bacillus coli communis*

usually predominates; in puerperal peritonitis the chief rôle is played by the *Streptococcus pyogenes*; while in those cases of peritonitis which apparently arise spontaneously the *Pneumococcus* or the *Gonococcus* is the chief exciting factor. In all those cases of peritonitis in which the infection comes from without the flora resembles that of ordinary surgical infections, except for the prominent part played by the colon bacillus. In those cases which arise by contiguity from some one of the neighboring organs the staphylococcus plays a chief rôle, except in the case of intestinal infection in which the colon bacillus alone or combined with the former is usually found.

Much discussion has taken place as to the pathogenic rôle of the colon bacillus in peritonitis. The pyogenic properties of this organism have been quite generally accepted, and there can be no doubt of the existence of a primary colon-bacillus peritonitis. In the majority of cases in which the colon bacillus is found pyogenic cocci are also present, and it is probable that in some of the instances in which this organism alone was found in the exudate it had overgrown the cocci. Barbacci in experimental work upon dogs found that the colon bacillus often outgrew the pyogenic cocci. Infections of the peritoneum with the colon bacillus occur through the bladder and female genital tract as well as directly from the intestine. There are still several questions to be settled before the exact pathogenic value of the colon bacillus can be fixed. Its relations to the pyogenic cocci need to be more definitely determined in regard to the part played by each as primary excitants of inflammation. Further, many of the cases regarded as colon-bacillus infections were diagnosed as such from the results of the bacteriological examination made at autopsy some hours after death. As the colon bacillus may enter the peritoneal cavity after death and increase there, overgrowing other bacteria, it is necessary, in order definitely to determine the relation of this organism to a peritonitis, to make bacteriological examinations of the peritoneal exudate during life.

An effort has been made by a number of writers to make a bacteriological classification of peritonitis. Freund divided all cases of peritonitis into three classes: one due to pyogenic organisms, one to faecal bacteria, and the third to toxic substances. Bumm distinguished a septic, aseptic, and a specific peritonitis. The septic he divided into a streptococcus peritonitis and a putrid peritonitis, the latter not caused by any one form of bacteria but by a multiple infection. The aseptic peritonitis he regarded as due to mechanical, thermal, or chemical influences alone without bacterial agency. In the class of specific peritonitis he placed tuberculous and gonorrhœal peritonitis. Tavel and Lanz have offered a more complex classification based upon the anatomical origin of the infection, special kinds of peritoneal infection being derived from the stomach and intestine, the gall bladder and liver, the female genital tract, the kidneys, urinary bladder, etc., other forms still being derived from hæmatogenous infections and operations.

Flexner has reported a series of observations upon one hundred and six cases of peritonitis studied from the bacteriological point of view. The material was obtained at autopsy, cover-glass and aerobic cultures being carried out. Few anaerobic cultures were made and the pathogenic properties of the bacteria isolated were tested but rarely. In spite of this incompleteness of the investigation the results are of interest. Twelve of the cases presented the character of a primary peritonitis according to Flexner's definition. In all these cases there was a previous chronic disease. In two cases no micro-organisms were found; in nine cases there was a single infection, and in one case a multiple infection. The *Streptococcus pyogenes* was found five times, four times alone, and once in association with the colon bacillus; the *Staphylococcus aureus* and *albus* twice, the *Micrococcus lanceolatus*, *Bacillus proteus*, *Bacillus pyocyaneus*, and an unidentified bacillus occurred twice each.

The secondary cases Flexner divides into two classes: *exogenous* peritonitis and *endogenous* peritonitis. In the

former the infection entered from without (wound infection); in the latter the bacteria came in part or wholly from the intestinal tract. Thirty-four cases of the exogenous form were examined. Of these, 25 were mono-infections, nine were multiple. The following tables are taken from Flexner's article (*Philadelphia Medical Journal*, 1898):

MICRO-ORGANISMS FOUND IN CASES OF EXOGENOUS PERITONITIS.

	Total number of cases.	Alone.	Combined.
<i>Staphylococcus aureus</i>	15	12	3
<i>Staphylococcus albus</i>	3	2	1
<i>Streptococcus pyogenes</i>	10	5	5
<i>Bacillus coli communis</i>	7	2	5
<i>Micrococcus lanceolatus</i>	3	1	2
<i>Bacillus proteus</i>	1	0	1
<i>Bacillus pyocyaneus</i>	2	0	2
Unidentified organisms	3	0	0(?)

COMBINATIONS.

Number of cases.

<i>Staphylococcus aureus</i> and <i>Streptococcus</i>	1
<i>Staphylococcus albus</i> and <i>Streptococcus</i>	1
<i>Staphylococcus albus</i> and <i>Bacillus proteus</i>	1
<i>Staphylococcus albus</i> and <i>Bacillus coli communis</i>	1
<i>Streptococcus</i> and <i>Bacillus coli communis</i>	1
<i>Streptococcus</i> , <i>Bacillus pyocyaneus</i> and <i>Coli communis</i>	1
<i>Streptococcus</i> and <i>Bacillus pyocyaneus</i>	1
<i>Micrococcus lanceolatus</i> and <i>Bacillus coli communis</i>	1
<i>Micrococcus lanceolatus</i> and liquefying <i>Bacillus</i>	1

Of 60 cases of endogenous peritonitis 53 gave positive bacteriological results. Single infections occurred in 21 cases of these, and multiple infections in 37.

BACTERIA FOUND IN CASES OF ENDOGENOUS PERITONITIS.

	Number of cases.	Alone.	Combined.
<i>Bacillus coli communis</i>	47	9	38
<i>Streptococcus pyogenes</i>	39	7	32
<i>Staphylococcus albus</i>	4	2	2
<i>Staphylococcus aureus</i>	3	1	2
<i>Micrococcus lanceolatus</i>	4	1	3
<i>Bacillus proteus</i>	4	2	2
<i>Bacillus aerogenes capsulatus</i>	8	2	6
<i>Bacillus pyocyaneus</i>	3	0	3
<i>Bacillus typhosus</i>	3	0	3
Unidentified	3	0	3

COMBINATIONS.

Number of times.

<i>Streptococcus</i> and <i>Bacillus coli communis</i>	16
<i>Streptococcus</i> , <i>Bacillus aerogenes</i> , and <i>Bacillus coli</i>	2
<i>Streptococcus</i> and <i>Bacillus aerogenes capsulatus</i>	1
<i>Streptococcus</i> and <i>Staphylococcus aureus</i>	1
<i>Streptococcus</i> and <i>Bacillus typhosus</i>	2
<i>Streptococcus</i> and <i>Staphylococcus aureus</i> , <i>Bacillus typhi</i> , <i>proteus</i> and <i>coli</i>	1
<i>Streptococcus</i> and <i>Bacillus proteus</i>	1
<i>Streptococcus</i> and unidentified organism	1
<i>Bacillus coli</i> and <i>Micrococcus lanceolatus</i>	3
<i>Bacillus coli</i> and <i>Bacillus pyocyaneus</i>	3
<i>Bacillus coli</i> and <i>Bacillus aerogenes capsulatus</i>	2
<i>Bacillus coli</i> , <i>Staphylococcus aureus</i> , and <i>Bacillus aerogenes capsulatus</i>	1
<i>Staphylococcus albus</i> and orange <i>sarcina</i>	1
<i>Staphylococcus albus</i> and unidentified organism	1

The comparison of the table in the exogenous and endogenous forms is of interest. It will be seen that multiple infections are relatively more frequent with the endogenous form, and that the variety of bacteria is much greater. The streptococcus takes the place which the staphylococcus holds in the exogenous cases and the colon bacillus plays a much more important rôle. The small part which the pathogenic staphylococci seem to play in endogenous peritonitis is of clinical importance, inasmuch as the streptococic infections may be associated with metastasis. The infections in the exogenous cases resemble those of ordinary surgical or traumatic infections. Basing his conclusions upon the observations, Flexner would distinguish three forms of peritonitis: a primary or idiopathic form restricted to a small number of terminal infections; a second variety analogous

to surgical infections; and a third variety dependent upon disease of an intraperitoneal organ, whereby micro-organisms and other extraneous substances gain entrance to the peritoneal cavity, break down its resistance, and lead to infection.

Pneumococcic Peritonitis.—Cases of peritonitis due to the *pneumococcus* have been described by Frommel, Fraenkel, Charrier, Veillon, Beco, Bryant, Comby, Brun, Burkhardt, and others. Brun reports fourteen cases of pneumococcus peritonitis in children. The majority of the cases of peritoneal infection with the pneumococcus occur in young girls. The avenue of infection is through the genital tract. The peritonitis may or may not be associated with inflammations of other serous membranes. The infection is frequently localized in the pelvis. The prognosis is favorable in those cases in which the exudate becomes encysted by adhesions, but metastases and localizations of the micro-organism in other parts of the body may occur. The diffuse form is usually fatal. In the case of operative procedures in pneumococcus pyosalpinx the greatest care must be taken to prevent infection of the peritoneum since the peritonitis thus excited is usually very virulent. Pneumococcus peritonitis may also result from extension or perforation in the case of a pneumococcus appendicitis. The relation to pneumonia and arthritis has been mentioned above. It is of importance in the diagnosis of this condition to bear in mind the fact that after death the pneumococci may entirely disappear from the peritoneal exudate, the colon bacillus or some other organism being left. Cases have been reported in which the examination of the pus from the peritoneal cavity during life, or soon after death, showed the presence of pneumococci in great numbers, while examinations made twenty-six to forty-eight hours later showed only the presence of intestinal bacteria.

Gonorrhœal Peritonitis.—The occurrence of an acute general peritonitis caused by the *Gonococcus* is now firmly established, and the condition is probably not infrequent in women affected with gonorrhœa of the internal genitals. Wertheim in opposition to Bumm was the first to maintain that gonococci may multiply within the peritoneal cavity and excite there an inflammation which may spread over the entire peritoneum. An increasing number of such cases is being reported. The view of Bumm and others, that the *Gonococcus* finds no favorable soil upon serous surfaces, and that its growth upon the peritoneum is slight and localized has been completely overthrown by recently reported cases. The infection of the peritoneum with the *Gonococcus* occurs chiefly in women, although cases of gonorrhœal peritonitis in men have been reported by Jadassohn, Horowitz, von Zeissl, and others. In the female the infection usually proceeds from the tubes. In the case of an infection of the woman with very virulent gonococci there may develop suddenly a most severe general peritonitis. The passage into the peritoneal cavity, from the mouth of the tube, of pus rich in gonococci always excites a general peritonitis; if the flow is small, and if but few gonococci are present in the pus, or if these are reduced in virulence a local peritonitis is usually set up. Gonococcic peritonitis is relatively more frequently a complication of gonorrhœal vaginitis and vulvitis in young girls. Such cases are unfortunately not rare in some of our large cities. The belief held by certain of the lower classes that gonorrhœa in the adult may be cured by rubbing the male organ over the external genitals of young girls is probably responsible for some of these cases. The peritoneal affection may appear as a mild or severe acute general peritonitis, or it may run a latent course as a chronic inflammation. The prognosis in these cases is always serious. Recovery may be followed by sterility.

PATHOLOGY.—The pathological changes found in the peritoneum in inflammation of this membrane are essentially the same as those occurring in inflammatory processes of the pleura and pericardium. According to the duration of the inflammation there may be distinguished an *acute*, *subacute*, or *chronic* peritonitis. According to the extent of the membrane involved a peritonitis may be

local or circumscribed, general or diffuse. A localization of the inflammation in the pelvis is generally spoken of as a *pelvic peritonitis*, in the neighborhood of the appendix as *peri-appendiceal*, over the spleen and liver as *perisplenitis, perihepatitis*, etc. According to the nature of the exudate there may be distinguished a *serous, fibrinous, purulent, hemorrhagic*, and a *putrid or gangrenous* peritonitis. Besides these pure types a variety of combinations, such as sero-fibrinous, sero-purulent, fibrino-purulent, sero-hemorrhagic, etc., occur.

Within certain limits the anatomical picture presented in all cases of peritonitis is essentially the same, but the appearances seen at autopsy or operation may vary greatly according to the chronicity, severity, and extent of the inflammation, the amount and character of the exudate, etc. The picture of a severe *acute general peritonitis* is, however, very characteristic. The abdomen is distended and tympanitic over the dome and dull over the flanks. When the cavity is opened the distended coils of intestine rise up through the opening, and an escape of gas may take place, even in non-perforative peritonitis. The serous surfaces are cloudy, in slight cases having the appearance of glass which has been breathed upon. Both the parietal peritoneum and the outer surface of the coils may be more or less reddened, injected, or even show ecchymoses. When the coils are lifted up and separated the reddened areas appear to be arranged in bands along the intestine. As a rule these reddened bands correspond to the spaces between the coils at those places at which the sides of the coils do not touch. The vessels of the serosa of these spaces are usually markedly hyperæmic, while at those points at which the coils do touch the vessels are less congested. According to Wilks and Moxon these spaces, which are triangular on cross section, form a system of communicating tubes through which the exudate may spread; and because of the lower resistance over these free surfaces absorption of the exudate is carried on here to a greater extent than elsewhere over the peritoneal surface. The loss of lustre and the cloudiness of the serous surfaces are due partly to the degeneration and desquamation of the endothelium, and partly to a layer of fibrin which is deposited over the surface. The latter may vary greatly in amount; in some cases the fibrin film may be so thin that it can be seen only as a slight cloudiness when examined by oblique light, or it may be made evident by rubbing off the delicate coating with a damp cloth or by scratching the serosa with the edge of the knife. In other cases the serosa may be covered with a thick, grayish, yellowish, yellowish-gray or reddish-gray exudate which may extend over the coils in a sheet, or in strings or bands of varying size, or appear as flakes scattered over the dull, lustreless surface. The fibrin may bind the coils more or less firmly together; in acute cases such adhesions are easily separated by the fingers, but in older cases the adhesions become organized to a greater or less extent, and so firm that they cannot be torn. The spleen and liver may become entirely covered by fibrinous sheets, or tags and flakes of fibrin may be scattered over their capsules. The amount of fibrin may be much greater in some parts of the cavity than in others, and by causing adhesions between neighboring structures may shut off portions of the cavity and confine the fluid exudate to certain regions.

Free fluid is usually present in the dependent portions of the cavity, in the flanks, pelvis, and the pockets between the coils. The amount varies greatly, sometimes many litres (20-40) causing a great distention of the abdomen, while at other times only a small amount is present. The fluid is always more or less cloudy or opaque, but varies in character according to the nature of the exudate, the character of the infection, the occurrence of perforation, etc. It may be serous, purulent, hemorrhagic, fibrinous, putrid, etc. In the great majority of cases it is fibrino-purulent, a pure purulent character rarely occurring, although a purulent character usually predominates. Rarely is it serous or sero-purulent. It is very often putrid (perforative peritonitis), and is then sanious, greenish, or grayish, having a

gangrenous odor, and may contain gas bubbles. Except in the case of tuberculosis or carcinoma a hemorrhagic exudate is very rare. The distribution of the exudate is generally very irregular owing to fibrinous adhesions. It usually collects in greatest amounts in the pelvis, flanks, splenic and hepatic regions, and in the deeper parts of the two hypochondriac regions. It often becomes encapsulated by fibrinous adhesions between the coils themselves, or between these and the abdominal wall or some one of the abdominal organs. The omentum often plays an important part in the encapsulation of exudates of small size in the appendix region and in the neighborhood of perforating ulcers of the intestine. Large collections of exudate are often found between the liver and the diaphragm; when of a purulent character and encapsulated from the other portions of the cavity the condition is often spoken of as a *subdiaphragmatic abscess*. Gas is particularly likely to collect in this region. In some cases the liver may be pressed tightly against the diaphragm, its diaphragmatic surface flattened and dry. The exudate often follows along the tubular spaces between the coils, so that the exudate from a pelvic peritonitis may pass under the lower coils of the ileum into the cæcal region and upward along the ascending colon to the right hypochondrium, then along the lesser curvature of the stomach to the cardiac end. In these regions the exudate may collect in large amounts, while elsewhere in the cavity there may be scarcely a trace of peritonitis. Not infrequently the exudate may become completely shut off from the cavity by fibrinous adhesions, which becoming organized, finally form a fibrous connective-tissue capsule enclosing the exudate, which is either absorbed, organized, or undergoes inspissation or calcification. As mentioned above, the omentum plays an important rôle in such encapsulations, which are most often seen in the neighborhood of the appendix and the female pelvic organs. In the case of a perforative peritonitis the exudate may contain, in addition to the purely inflammatory products, also stomach or intestinal contents, bile, urine, etc.

In the more severe cases the entire intestinal wall may be involved, becoming swollen, oedematous, and easily torn. Even in the light cases the subserosa is oedematically swollen and may be easily stripped off from the muscularis. The muscle coats may be completely paralyzed; hence the occurrence of marked tympanites, general or local. On opening the stomach and intestines the mucosa is usually found to be pale, swollen, and oedematous. Likewise the superficial portions of the liver, spleen, gall bladder, etc., are oedematous and swollen, often appearing as if macerated. The gall bladder and the lower edge of the liver in particular may show an extreme oedema. The tissues of the mesentery are swollen, moist, and more easily torn than normally. The mesenteric and retroperitoneal glands are usually pale, soft, and enlarged. Even the muscles of the abdominal wall may be pale and oedematous, and the parietal peritoneum can be easily stripped from its attachments. The omentum is swollen, injected, and oedematous. It is very frequently rolled up into a thick mass, but in the case of surgical or perforative peritonitis it is usually more or less adherent to the site of injury. It may be covered with a thick layer of fibrin and may aid in the encapsulation of the exudate. The diaphragm is usually pushed up to the third or even second rib; the lungs show partial atelectasis, particularly the lower lobes; and the heart is pushed upward and more or less to one side.

Although the changes just described apply to the great majority of cases of peritonitis, yet the limit of variation is great, in so far as the appearances presented by individual cases are concerned. A pure *serous peritonitis* (*peritonitis serosa*) is relatively infrequent. Some fibrin is almost always present, so that the exudate should be more properly termed sero-fibrinous. The fluid exudate is yellowish, slightly cloudy, and contains but few cells, but fibrin flakes are found floating in it. Over the peritoneum there is usually a delicate film of fibrin. A pure *fibrinous peritonitis* is not common as a general process,

but is often seen as a local peritonitis. The serosa is cloudy, dry (*peritonitis sicca*) and covered with sticky fibrin.

When the number of cells in the exudate is so great as to cause a turbidity, the peritonitis may be styled *purulent* (*peritonitis purulenta*). A pure purulent peritonitis is also rare, the character of the exudate being usually that of a *fibrino-purulent* inflammation. The coils are usually fastened together by masses of fibrin, while in the pockets between them a relatively pure purulent exudate is found, usually in large amounts (20-30 litres). The so-called *peritonitis ulcerosa* is a misnomer, the appearances of ulceration over the surfaces of the abdominal organs and the parietal layer of the peritoneum being due to a loss of substance through erosion and pressure. In such cases the purulent exudate may perforate into the stomach, intestine, ureter, bladder, uterus, or through the diaphragm or abdominal wall (*secondary perforative peritonitis*). In the last-named case the perforation is usually located at the navel. This event happens more frequently in children than in adults.

In the case of *putrid peritonitis* the exudate has a foul odor and is irritating to the skin of the operator or prosecutor. In color it varies from dirty-green to brownish. The fibrin of the exudate and the serosa itself may be likewise dark-colored. Gas may be present in the cavity, and the odor of hydrogen sulphide is often very pronounced even when no perforation has occurred. In the case of a perforation of stomach or intestine food remains or faeces may be found in the exudate. Brownish masses are also sometimes present; on microscopical examination they are found to consist of colonies of bacteria.

An acute *hemorrhagic peritonitis* is rare. It is usually associated with carcinoma or tuberculosis, but occurs also in morbus maculosus Werlhofii and in scurvy. Through the presence of hydrogen sulphide in the exudate the blood pigment may become converted into a hydrogen-sulphide compound, giving a gray or slate color to the exudate and serosa (*pseudomelanosis*). Friedreich has described an especial form of hemorrhagic peritonitis under the name of *hematoma peritonei*. In such cases the peritoneal surface is covered with layers of blood clot which are becoming organized, the condition being analogous to the subdural hæmatoma.

Circumscribed peritonitis presents practically the same appearances as the general form, except in being localized through the rapid formation of firm adhesions which prevent the inflammation from spreading (*peritonitis adhesiva*). These adhesions may quickly become organized. Circumscribed peritonitis occurs most often as a perityphilitis (peri-appendiceal) dependent upon perforation of the appendix, and as a pelvic peritonitis (pelveo-peritonitis) due to diseased conditions of the uterus and its appendages. It may be caused also by perforative processes (ulcer, new growths, etc.) of stomach, intestine, gall bladder, etc., by splenic infarction, hepatic abscess, and other local inflammations of the intraperitoneal organs. The so-called subdiaphragmatic abscess is an encapsulated purulent peritonitis. Similar encysted collections of exudate may be found in any part of the peritoneal cavity, but are more frequent in the regions named. Gonococcal peritonitis is usually circumscribed in the pelvis. The part which the omentum plays in the encapsulation of a local peritonitis has been mentioned above. Through its aid many cases of perforation peritonitis, particularly in the case of the appendix, are restricted to a narrow area. The frequency with which omental adhesions are formed about the appendix, tubes, perforating ulcers, new growths, etc., is evidence of its very great service in limiting peritonitis.

Complications.—The complications of acute peritonitis are many and important. Perforation of the peritoneal exudate into some viscus or through the abdominal walls has been mentioned. Occasionally the pus may break through into two neighboring coils of intestine at the same time, giving rise to the so-called *fistule bimucosa*. Fatal hemorrhage may follow perforation into an abdominal blood-vessel. Metastasis may occur and a gen-

eral pyæmia may result. It is not uncommon in the case of a severe acute general peritonitis to find at autopsy a beginning pleuritis, pericarditis, or meningitis. Sometimes all the serous membranes may be equally involved (panserositis). Such pathological findings are seen most frequently in puerperal peritonitis.

Microscopical Appearances.—Sections through an acutely inflamed peritoneum present changes which are analogous to those of inflammations of other serous membranes. The surface of the membrane is covered with a more or less thick layer of fibrin containing a varying number of leucocytes. The latter usually show karyorrhexis, the diffusion of the chromatin throughout the fibrin causing the latter to stain bluish. Beneath the exudate the endothelium is degenerated, necrotic, or desquamated. The connective tissue of the basement membrane is oedematous and infiltrated with leucocytes. The lymphatics are greatly dilated and contain fibrin and large numbers of leucocytes. The blood-vessels are also greatly congested and filled with leucocytes. The endothelial cells of both lymph- and blood-vessels are usually somewhat swollen. Scattered hemorrhages of small size may also be found. The subserosa is usually actively involved, the connective tissue being oedematous and infiltrated with leucocytes; the vessels are congested and small hemorrhages may occur. Fibrin threads may be found in the intercellular spaces of both serosa and subserosa. The muscularis is involved to a much less extent. Its vessels are congested and the intermuscular connective tissue is more or less oedematous and contains an increased number of leucocytes. In severe cases the nerve cells of the intestinal wall may present various changes, such as vacuolation, hydropic degeneration, chromatolysis, etc. In the later stages of the inflammation evidences of proliferation are found in the endothelial cells of the blood- and lymph-vessels and in the connective-tissue cells of the serosa and subserosa. Fibroblasts wander out into the fibrin of the exudate and a new formation of capillaries takes place. Even in attacks of peritonitis lasting but five to seven days the organization of the exudate may have advanced considerably. In the further progress of the disease connective-tissue adhesions and false membranes may be formed, or marked thickenings of the peritoneal surfaces may result. Should complete healing take place the newly formed connective tissue becomes scar-like and hyaline, and marked retractions of the omentum and mesentery may be caused. The remains of old organized fibrinous exudates are most frequently seen in the form of tendinous patches or small pearly nodules over the surface of the spleen, liver, or intestine. Extensive thickening of the pelvic peritoneum may result from the healing of circumscribed peritonitis in this region. During the stage of active fibroblastic proliferation such a large mass of granulation tissue may be formed that in the case of a circumscribed peri-appendiceal peritonitis a tumor may be produced which may be mistaken clinically for a malignant neoplasm, and even when examined microscopically might be mistaken for a sarcoma. Such tumor-like masses may also be found in the omentum. Should healing take place the tumor may gradually contract and finally entirely disappear ("disappearing tumor"). The presence of exudate not yet organized, the large number of polymorphonuclear leucocytes showing karyorrhexis, the hypertrophic character of the endothelium of the numerous capillaries, the presence of many plasma cells and phagocytes, the development in areas of a fibrous intercellular substance, etc., are among the points to be considered in making a microscopical diagnosis of tissue removed from such tumor-like formations.

Subacute Peritonitis.—In cases running a slower course the amount of exudate is usually less than in the acute forms, although in some cases in which it is more serous in character the amount may be very large. The adhesions are firmer, organization having progressed to a greater extent. The serosa is thickened, roughened, and wholly lustreless, and is often grayish or slate-colored. The injection of the blood-vessels is much less, and there

is also less œdema of the subserosa. Exacerbations, which are very likely to occur, give the appearances of an acute inflammation. Microscopically the exudate covering the serosa is found to be partly organized, and there is a fibroblastic increase of tissue. The cells of the exudate may show fatty or hydropic degeneration.

Chronic Peritonitis.—Chronic peritonitis may follow an acute process or it may develop insidiously. The changes seen in chronic peritonitis are essentially the same as in the acute process, the chief difference being in the more advanced organization of the exudate with resulting firm adhesions and formation of false membranes, tendinous patches, etc. When numerous adhesions are formed the condition is termed *peritonitis chronica adhesiva*. The capsule of the liver and spleen may be greatly thickened and hyaline (chronic perihepatitis, chronic perisplenitis). Scar-like thickenings and retractions of the omentum and mesentery may be found (*peritonitis chronica retrahens*), and in the former there may be produced tumor-like masses of granulation tissue. It is usually rolled up above the level of the umbilicus. Marked deformities of the intestine and intraperitoneal organs may be produced by the contraction of the new-formed connective tissue (*peritonitis deformans*). Partial or complete stenosis of the intestine, common duct, ureters, tubes, etc., may result from the contraction or pull of band-like adhesions. Incarceration of portions of the intestinal coils in hernia-like sacs formed by adhesions may also occur. Inasmuch as exacerbations are not infrequently seen in chronic peritonitis the picture of a recent exudation may be added to that of an older process. The *hematoma peritonei* of Friedreich mentioned above is associated particularly with a rare form of chronic hemorrhagic peritonitis. Chronic peritonitis may be local or general; the former is the more common. The inflammation may be dry, or a sero-fibrinous exudate may be present; less frequently the exudate is hemorrhagic or purulent.

Local chronic peritonitis is seen most often in the hepatic region (cirrhosis, gall-stones, syphilis, etc.), in the splenic region (perisplenitis), and in the pelvis of the female. In prostitutes a local chronic pelveo-peritonitis is nearly always present in the form of adhesions. The appendix region, the neighborhood of gastric and intestinal ulcers, hernial sacs, etc., are also frequent seats of chronic peritonitis.

Attention has recently been directed to the condition designated "*chronic multiple serositis*" or "*multiple progressive hyaloseritis*" which is characterized by a slowly progressive hyperplasia of the serous membranes with secondary hyaline changes. In the case of the peritoneum the condition is usually most marked over the capsule of the liver or spleen (chronic perihepatitis, chronic perisplenitis). The thickened and hyaline capsule presents an appearance resembling the icing of a cake ("*Zuckergussleber*" of Curschmann, "*iced liver*"). An obliterative pericarditis or pleuritis may or may not be coincident with the peritoneal condition. The capsules of the liver and spleen may be involved at the same time or either one may alone show the change, or the condition may be diffuse throughout the entire extent of the peritoneum, or it may occur as a part of a multiple affection of the serous membranes. When affecting chiefly the liver capsule the condition may be the result of a local chronic peritonitis, an acute or subacute hepatitis, chronic mediastinopericarditis, or a chronic obliterative pleuritis. It may also be a part of a Glissonian cirrhosis, perhaps associated with syphilis or tuberculosis. The affection of the splenic capsule is usually the result of a local chronic peritonitis, or is associated with syphilis or tuberculosis. Chronic hyaloseritis is essentially a hyperplastic inflammation, and is probably due to an infection with micro-organisms of a low virulence. In the majority of cases it is probably tuberculous. Microscopically the thickened splenic or hepatic capsule consists of laminated hyaline connective tissue, usually poor in cells, but occasionally containing groups of leucocytes or areas of unorganized fibrin. In some cases, at least, the

organization of a fibrinous exudate with subsequent hyaline change of the new connective tissue plays an important, if not the chief, part in the production of the condition.

Peritonitis Carcinomatosa.—Scirrhus carcinoma of the stomach or gall bladder may give rise to secondaries scattered diffusely throughout the peritoneum. The membrane at the same time presents the appearance of a chronic hyaloperitonitis, the entire serosa, intestinal and parietal, as well as the hepatic and splenic capsules, being greatly thickened, dense, and hyaline. Such a condition may very easily be mistaken for a simple chronic peritonitis, inasmuch as appearances suggesting malignancy may not be visible to the naked eye. The diagnosis in some cases can be made only on microscopical examination, since the primary growth may consist only of a dense thickening of the pyloric end of the stomach or of the gall-bladder wall and may not be recognized from the gross appearances. Microscopically the hyaline connective tissue of the thickened peritoneum is seen to contain small nests and cords of epithelial cells, corresponding to those of the carcinomatous infiltration at the primary seat. It is well to bear in mind the fact that the mesenteric and retroperitoneal lymph glands may contain large nests of cancer cells, so that the diagnosis of scirrhus carcinoma may be more easily arrived at by the examination of these glands. The peritoneal condition may therefore be regarded as of the nature of a diffuse carcinomatosis with secondary inflammatory changes. More or less fibrinous exudate may be present over the surface of the thickened membrane, and some free fluid may be present in the cavity.

Experimental Peritonitis.—A number of important experimental studies of peritonitis have been carried out by different observers, particularly with reference to the etiological factors of peritonitis. The part played by various bacteria and by such predisposing factors as chemical irritation, cold, etc., has been studied with the gain of much important knowledge. Other writers have recently studied the character of the cells found in the peritoneal exudate. Beattie has made experimental investigations along this line. After the injection of bacteria into the peritoneal cavity various cells appear in the exudate. Polymorphonuclear leucocytes appear in great numbers on the peritoneal surface, and are found abundantly in from six to fifty-four hours after the injection. In fatal cases they increase up to the time of death of the animal, but in non-fatal cases they diminish in from forty-eight to sixty hours. They act as the chief bacterial phagocytes. Mononuclear phagocytes are also found at all stages, but are most abundant from thirty-six hours onward. They are derived from the endothelium of the serous membrane, of blood-vessels, lymph vessels, lymph spaces, etc. They possess amoeboid motion, and are especially phagocytic to other cells, but may also take up bacteria. Great numbers of these cells are always found on the omentum, and Beattie regards them as the most important cells of the peritoneal exudate. The presence of large numbers of these cells, if they give evidences of active function, is a favorable sign. Since the omentum furnishes large numbers of the mononuclear cells in peritonitis this organ must be regarded as an important agent in protecting the body from infection by way of the peritoneum. Both the polymorphonuclear and mononuclear phagocytes are destroyed in the peritoneal sac, the former being largely ingested by the latter. In the case of peritonitis associated with secondary carcinoma of the peritoneum tumor cells may be found in the exudate in addition to the polymorphonuclear and mononuclear phagocytes. As a rule the cancer cells cannot be distinguished from the latter; but if numerous cell-division figures are present, especially atypical forms, it is very likely that such cells come from a new growth.

SYMPTOMS.—*Acute General Peritonitis.*—Peritonitis in the great majority of cases being a secondary disease the symptoms are modified to a greater or less extent by the original trouble. The onset in particular is modified.

Perforative peritonitis may occur suddenly in a person apparently in perfect health. Not infrequently the first intimation of the existence of a gastric or intestinal ulcer is the peritonitis following a perforation. In the case of perforative appendicitis the onset may be equally sudden. On the other hand, the symptoms of perforative peritonitis may be obscured in the case of intestinal tuberculosis, typhoid fever, intestinal obstruction, etc., by the severe local or general symptoms. A circumscribed peritonitis may also become gradually changed into a general condition, the change in symptoms not being so pronounced as to be noted. For example, a localized purulent perityphlitis or a purulent puerperal pelveo-peritonitis may become generalized. A pneumococcic peritonitis occurring in association with pneumonia or meningitis may have its onset obscured by the general symptoms.

In spite of these exceptions nearly every case of acute general peritonitis runs a clinical course so typical and characteristic that the recognition of the condition becomes a matter attended by little or no difficulty.

Prodromal symptoms may or may not occur. In the former case they consist of chills, prolonged and repeated chilly sensations, fever, loss of appetite, nausea, vomiting, thirst, diarrhoea or constipation, flatulence, etc.

Pain is the earliest definite symptom, and few cases of acute peritonitis exist without it. In patients who are extremely weak or whose minds are clouded, no complaint of pain may be made, and the condition may in this way escape notice. In nearly every case, however, the pain becomes the most marked and important symptom. It may be local, often referred to the region of the umbilicus, but later usually extends over the entire abdomen. The localization of the pain at the onset of the disease may have some diagnostic value in indicating the possible source of the inflammation, as, for example, in the case of gastric ulcer or a perforating appendicitis. The pain is usually excruciating in character, and may be constant, or it may occur with short remissions followed by exacerbations. Colic-like paroxysms sometimes occur. The abdomen is extremely sensitive, so that even gentle palpation, or even the weight of the bed clothes can hardly be borne. The patient assumes a position which relieves the tension of the abdominal muscles, lying on the back with thighs drawn up and shoulders elevated. Such a position may be maintained for days and weeks as long as the condition lasts. The pain is increased by deep inspirations, voluntary movements, and probably also by intestinal peristalsis. The patient fears particularly such movements as vomiting, coughing, sneezing, defecation and urination, etc. The character of the pain is sometimes described as burning, boring, tearing, lancinating, etc., without much light being thrown upon the conditions causing the especial character. The passage of gas through the coils probably plays an important part in producing the painful attacks. Though in the majority of cases the pain is most severe below the umbilicus, in cases of perforation of the stomach the pain may be referred to the shoulders, back, or chest. In the earlier stages of peritonitis following appendicitis the pain may sometimes be referred to the testicle or the penis. Mackenzie believes that the pain which is caused by pressure over the abdomen is entirely due to muscular and cutaneous hyperæsthesia, the peritoneum itself being devoid of sensory nerves. The board-like hardness of the abdominal muscles in peritonitis he holds to be the result of a violent stimulation passing from the affected organs of the peritoneal cavity to the spinal cord, where the irritation spreads, affecting not only the centres of the sensory nerves, but also those of the muscular nerves. When the patient is at perfect rest the pain may be slight or may even entirely disappear.

The *respiration* is very superficial, rapid, and wholly costal in type. The speech usually becomes an almost imperceptible whisper, occasionally hoarse and high-pitched, resembling the so-called *vox cholericæ*. When the attack is fully established the patient presents a very characteristic appearance, the expression is anxious, the

face pinched and the eyes are sunken, the Hippocratic facies being seen in this affection more often than in any other disease except cholera. The severity of the pain is usually expressed by the patient's face; in severe cases the eyes are glassy and staring. Consciousness remains preserved usually until the last; rarely there is delirium, coma, or convulsion at the end.

The abdomen quickly becomes distended, the distention becoming gradually more and more marked, and sometimes reaches such an extent that it seems that the abdominal wall must give way. The skin over the abdomen is smooth, shining, thinned, the superficial veins appearing as blue lines. Fresh lineæ albicantiæ may be seen over the surface. The abdominal muscles are stretched and often of a board-like hardness. The distention is due to the intestinal tympanites, which is sometimes so great that complete paralysis of the intestinal musculature results. The distended coils of intestine can sometimes be traced through the abdominal wall. The more lax the abdominal wall before the beginning of the peritonitis the greater will be the distention; hence the distention is most marked in the puerperal cases. When the abdominal muscles are well developed and the abdominal wall is tense, the convexity may not be great. In some cases the wall may be as hard as a board and flat or even somewhat concave. In the latter case the diagnosis may be very difficult. In the later stages the abdominal distention is increased by the fluid exudate.

Vomiting is an almost constant symptom in peritonitis. It usually begins early in the disease and causes great pain. At first the vomitus consists of food remains, later it consists chiefly of a yellowish bile-stained fluid, and finally becomes greenish. Occasionally the vomitus is brownish-black and possesses a slight faecal odor. The attacks may be spontaneous or follow the taking of food. In the former case the vomitus consists usually of greenish mucus. Eructations of gas usually accompany the vomiting. The frequency and intensity of the vomiting vary. In some cases nothing can be retained upon the stomach, and the patient's strength is very quickly lost. The cause of the vomiting is not clear; it is probably partly reflex and partly due to pressure upon the stomach. In those cases in which the vomitus has a faecal character the autopsy usually discloses no intestinal obstruction. It is therefore probable that the condition is due to the paralysis of the intestinal musculature and to the pressure upon the intestine. Toward the close of the attack the vomiting may be replaced by painful *hiccoughs*, which are a source of great torture to the patient. It is probable that this is due to the involvement of the peritoneal surface of the diaphragm. In those cases in which the vomiting is kept up to the end some of the vomitus usually enters the respiratory tract and may give rise to an aspiration pneumonia or gangrene of the lung.

Peritonitis not infrequently begins with *diarrhoea*, which in some cases is associated with tenesmus, or assumes a dysenteric character. The paralysis of the intestinal musculature soon leads to *constipation*, so that this condition becomes an almost constant feature of the disease.

The *tongue* is usually coated, grayish-white or brown; in cases of obstinate vomiting it may be clean and red or fissured. A very disagreeable fœtor is usually present, sometimes almost faecal in character.

After the chill the body temperature usually rises, reaching 104°-105° F. or higher, but later usually falls. The type of the *fever* is very varied; it may be continuous, intermittent, or remittent. The skin may be cool, while the rectal temperature is high. In the case of collapse the temperature may fall even to subnormal, and the body may be covered with an abundant cold perspiration. Just before death the temperature may rise again and reach a very high point.

The *pulse* is usually very frequent, the increase in rate being out of proportion to the fever, 120-140 per minute not being uncommon. The pulse is at the same time

small and soft, and in very severe cases may become imperceptible.

The number of *respirations* is increased, 30–40 per minute. The increased rate is due partly to the fever, partly to the high position of the diaphragm, and partly to the pain attending abdominal breathing. As mentioned above, the type is costal and the breathing superficial. The cessation of movement of the diaphragm is regarded as a bad sign, some writers considering the prognosis hopeful as long as an inspiratory excursion of the diaphragm can be felt, this being taken as a sign that the peritonitis is not wholly diffuse.

The *subjective* symptoms are chiefly pain, uncontrollable thirst, shortness of breath, and anxiety.

Percussion gives a tympanitic tone over the distended intestine. Dulness over the dependent portions is usually not made out until after considerable exudate has collected. When the tympanites is very marked a large amount of effusion may be present without its being detected on percussion. A change of level of the dulness with change of position does not always take place; the adhesions between the coils preventing the movement of the exudate. Moreover, there is usually too much pain to permit of a careful examination. The liver dulness is diminished, the upper border being pushed upward to the fifth or fourth rib. The splenic dulness cannot usually be made out. The heart is pushed upward, the apex beat dislocated upward and to the left. The movements of the heart in the intercostal spaces are more prominent than normal.

Auscultation of the abdomen does not throw much light upon the condition. Gurgling and splashing sounds may be heard in the intestines. Occasionally friction sounds may be heard, but these are not so common as in pleuritis or pericarditis. In pneumoperitonitis splashing sounds may be produced by shaking the patient. The heart sounds may have a metallic resonance in the case of extreme tympanites. The pulmonary second sound is usually accentuated.

The *urine* is usually diminished in amount, dark, strongly acid, of high specific gravity, and sometimes contains a small amount of albumin. The amount of indican present may be much greater than usual.

Certain writers claim that there is a *local increase of temperature* in the abdominal wall, and that this fact constitutes an important diagnostic factor. The normal temperature of the surface of the abdomen is about 35.5° C.

In the case of *pneumoperitoneum* due to perforation or to formation of gas within the cavity the hepatic dulness is obliterated. The liver dulness may, however, disappear when there is no gas in the cavity; but if the patient is placed upon his left side a clear percussion tone will be heard at the seventh or eighth rib in the right axillary line in the case of pneumoperitoneum. In other cases dulness will be found at this region. The disappearance of the liver dulness anteriorly when pneumoperitoneum does not exist is due to the tilting backward of the organ and the presence between it and the abdominal wall of a loop of distended intestine.

The *course* of an acute general peritonitis is usually very rapid. The most severe cases may terminate fatally within thirty-six to forty-eight hours, while the average case usually lasts five or six days. Since the etiological factors vary so greatly no absolute statements can be made regarding the clinical course. The peritonitis occurring as the result of gastric or intestinal perforation is usually quickly fatal, but much is to be hoped from the surgical treatment of these cases. Puerperal septic peritonitis is likewise usually fatal. Pneumococcic peritonitis is also likely to terminate more or less quickly in the death of the patient. The peritonitis which occurs in connection with arthritis, as well as in all other cases in which the exudate is serous or sero-fibrinous, is much more likely to end in recovery.

In the fatal cases *death* may occur suddenly as if from shock; or in the case of extreme tympanites the high position of the diaphragm may cause death from suffo-

cation. In some cases the final picture is that of a general sepsis or pyæmia. In the great majority of cases the pulse becomes more rapid, the vomiting persists, the bodily powers are quickly exhausted, and the patient dies with symptoms of collapse. In such cases the temperature usually becomes subnormal as the end approaches.

In other cases of less frequent occurrence the disease may drag itself out over weeks and months, assuming the characteristics of a subacute or chronic process. Various complications may occur during such a prolonged course. Rupture of the exudate into the gastro-intestinal tract or through the abdominal wall, etc., is most likely to occur in such cases. In the event of such perforation into the stomach, pus will be found in the vomitus; when into the intestine the pus will appear in the stools; when into the urinary tract the urine will show a sediment of pus; when into the respiratory tract the sputum will be abundant and purulent. In the event of a rupture through the abdominal wall redness, swelling, and œdema will first appear at the affected spot, the skin becomes thinned, fluctuation occurs, and pus finally seeps through small fissures, or an opening of large size may be formed, through which the pus may be forced in streams during coughing, etc. The navel is the most common seat of perforation. In some cases the pus burrows beneath the skin for some distance before it finally breaks through. In other cases some of the exudate may be absorbed or encapsulation may take place. Exacerbations are frequent and death may take place finally from general marasmus. General dropsy, bed-sores, albuminuria, etc., characterize the course of such cases.

In the mild cases of general peritonitis following labor, abortion, or menstruation recovery may occur. Even in those cases in which the disease runs a rapid and favorable course disturbances of the digestive tract usually develop, and the patient may die later from intestinal obstruction caused by the contraction of adhesions. A favorable prognosis should not be too hastily given in such cases. Nevertheless, complete recovery may result after a year or longer, even in very severe cases.

Acute Circumscribed Peritonitis.—The local symptoms of this form are similar to those of the general process, but are more limited. The vomiting is not so severe or so persistent as in the general inflammation. Though the general weakness is marked the symptoms of collapse do not occur to the same extent as in general peritonitis. An irregular fever is usually present, running a course suggesting that of a pyæmic affection. The condition is usually very chronic. Many patients die from general debility. Spontaneous evacuation of the encapsulated exudate may take place through perforation into the gastro-intestinal tract, pleura and lungs, abdominal wall, etc. Should the perforation take place into the remaining portion of the peritoneal cavity the peritonitis may become diffuse. According to the location of the inflammation (perisplenitis, perihepatitis, perityphlitis, perimetritis, peripancratis, perigastritis, epiploitis, mesenteritis, etc.) various symptoms may arise through the disturbance of function of the affected organ. Pain is usually felt in the affected region. The physical signs are local tumor, dulness, fluctuation, peritoneal friction, etc.

Of the various forms of acute circumscribed peritonitis the condition known as *subphrenic abscess* deserves especial attention. It is due to an encapsulated collection of purulent exudate between the upper surface of the liver, stomach, or spleen, and the diaphragm. Owing to the paralysis of the diaphragm the tumor may rise high into the thorax and may be mistaken for a pleural effusion, especially since a secondary pleuritis is usually present. Hepatic abscess, splenic infarction, splenic abscess, rupture of echinococcus cysts, and gall stones are the more common causes of the condition, but it is not a rare complication of perforating appendicitis.

Perforation Peritonitis.—The peritonitis due to perforation may be local or general. It may run a very

acute course, but when circumscribed is more likely to be chronic. In the case of the sudden perforation, as, for example, of the stomach, intestine, cystic tumor, etc., the patient may feel a sharp tearing sensation, as if something had given way within the body. The severest symptoms of collapse may immediately result. The abdomen may be contracted, hard as a board, and even scaphoid. The slightest touch causes extreme pain. Death may take place within a few hours. In other cases the entrance into the peritoneal cavity of stomach contents, feces, bile, etc., excites a general peritonitis with symptoms as described above. In the case of perforation of the gastro-intestinal tract gas may also enter the cavity, and the picture of a pneumoperitonitis be presented. The liver and splenic areas of dullness are obliterated unless these organs have become attached to the anterior abdominal wall by means of adhesions. Succussion sounds may be produced, and the respiratory sounds may acquire an amphoric quality.

Puerperal Peritonitis.—This dreaded complication usually appears at from the third to the fifth day after labor. Safety from the condition is usually assumed if the woman reaches the end of the second week without its occurrence. The pain is usually much less intense than in the other forms of general peritonitis, and the tympanites more marked. Chills occur more frequently than in other forms and diarrhoea is almost always present, the discharges often becoming bloody and of the character of a dysentery. The vomiting is especially obstinate. The lochial discharges often become offensive. The peritoneal exudate is usually more abundant and more purulent in character than in other forms, and not infrequently becomes putrid. The mortality is great, death taking place with symptoms of general sepsis usually between the fifth and twelfth days.

Infantile Peritonitis.—*Fetal* peritonitis occurs between the seventh and ninth months of intra-uterine life. Syphilis is the chief etiological factor. Infection of the umbilicus may lead to a *peritonitis neonatorum*. The children of mothers suffering from puerperal sepsis are especially likely to become infected. In addition to the local symptoms of distention, pain, etc., there is usually a picture of general sepsis or pyæmia. The condition is almost always fatal. A peritonitis may also develop in infants and young children (*peritonitis infantum*) as the result of syphilis, or of infection with pyogenic organisms, the pneumococcus, gonococcus, etc. In the great majority of cases peritonitis in young children is the result of appendicitis. In peritonitis which occurs in young girls the possibility of a gonococcal infection should always be borne in mind and the genital passages examined for the existence of such disease. Non-gonococcal vulvo-vaginitis rarely spreads to the peritoneum. Pneumococcal peritonitis is more common in girl than in boy infants. The infection is probably through the genital tract. The onset is usually very sudden, with abdominal pain, fever, and vomiting. The course of the affection is very similar to that of pneumonia, the active symptoms subsiding in from seven to ten days, but the abdomen remains distended, and later the presence of an exudate becomes manifest. The prognosis in the cases of general infection is not good, but when the inflammation is localized in the pelvis it is more favorable.

Chronic Peritonitis.—In the majority of cases chronic diffuse peritonitis is the sequela of an acute inflammation, although such an occurrence is relatively rare. Usually no sharp line can be drawn between the two; the symptoms of an intense acute process gradually abate and are replaced by those of a chronic type. In some cases the chronic inflammation develops as the sequela of a number of acute attacks; in others the onset is slow and insidious. The pain, abdominal tenderness, and distention are never so marked as in the acute cases. The distention is usually moderate and often asymmetrical, certain coils of intestine being especially prominent. Sometimes the abdomen is flat or even scaphoid, the walls are hard and board-like. On palpation the thickening of the omentum and mesentery, as well as the fibrous

adhesions between the coils, may be made out as tumor-like masses or as uneven prominences. When an effusion is present palpation may be negative. A friction rub may occasionally be felt. In some cases the abdomen may be so tense that nothing can be felt through it. Cases of chronic peritonitis, not due to tuberculosis or complicated with other conditions, do not usually show much exudation. The course is very protracted. Recovery may follow the absorption and organization of the exudate, or its escape by perforation from the cavity. Death usually results from general marasmus. The healing of the inflammation may be followed later by stenosis and intestinal obstruction, which may result fatally. Occlusions of the common duct by the contraction of adhesions may cause a chronic obstructive jaundice.

A peculiar form of chronic serous peritonitis occurs in children, appearing under the form of a chronic ascites. It occurs most frequently between the ages of two and ten, and in girls at the age of puberty. The abdomen is distended by the exudate, which is usually quite abundant, serous in character, and freely movable. The affected children are anæmic, more or less weak, but do not lose much in weight and do not suffer pain. The lower extremities may become œdematous. The exudate may apparently entirely disappear and then return. The course may last many months and may terminate in complete recovery. The exact nature of the affection is unknown. Trauma, inflammation of the gastro-intestinal tract, lymph glands, and genital tract, etc., have been adduced as etiological factors. It is possible that the condition represents an infection of the peritoneum with tubercle bacilli of low virulence. In the fatal cases death results from an increasing marasmus.

TUBERCULOSIS OF THE PERITONEUM.—Tuberculous disease of the peritoneum is of especial interest because of its peculiar clinical course and the fact that the condition may undergo spontaneous healing after laparotomy. A distinction is drawn by some writers between pure tuberculosis of the peritoneum and a tuberculous peritonitis; but such a distinction, while based upon pathological grounds, has but little practical value, the first condition rarely presenting clinical signs.

Simple tuberculosis of the peritoneum without accompanying inflammation or exudation is usually secondary to an acute miliary or chronic pulmonary tuberculosis. It may be secondary also to tuberculosis of the bronchial or subperitoneal lymph glands, genito-urinary tuberculosis, tuberculosis of the pleura, adrenal bodies, etc. In the great majority of cases the infection of the peritoneum proceeds from tuberculous ulcers of the intestine or caseating mesenteric glands. In rare cases it may be primary. Small grayish tubercles are found scattered over the peritoneum. On microscopical examination they consist of epithelioid cells and numerous giant cells containing tubercle bacilli. Caseating centres may be seen in the larger ones; but inflammatory changes in the neighboring peritoneum are usually wanting. The tubercles are almost always more numerous in the omentum. When very small the tubercles may not be recognized at operation or autopsy; the larger ones are recognized by their grayish color and yellowish centres. Though often very numerous the tubercles are usually circumscribed. There are no symptoms, the condition usually being discovered at autopsy, or in the event of a laparotomy.

Tuberculous peritonitis—tuberculosis with inflammation and exudation—exists in a great variety of forms which have been variously classified by different authors. The most common forms are: *acute miliary tuberculosis* with sero-fibrinous or sero-hemorrhagic exudation; *chronic tuberculous ascites* with small tubercles which show little caseation; *chronic fibro-caseous tuberculous peritonitis* with purulent or fibrino-purulent exudate; *chronic hyperplastic tuberculous peritonitis*; *chronic fibroid tuberculosis* with little or no exudation, the serous surfaces being fastened together by adhesions.

The appearances at autopsy or operation may vary

greatly. In the majority of cases two types predominate: the *adhesive* form and that with *free fluid exudate*. The former is the more common. The coils and the abdominal organs are matted together and to the parietal peritoneum by numerous firm adhesions, in which there are found numerous tubercles or caseous masses. The spaces between the adhesions are filled with a purulent, fibrino-purulent, or hemorrhagic exudate, or, if perforation into the bowel has occurred, with exudate containing faecal material. Such perforation is not uncommon and faecal fistulae may be formed. The adhesions between the liver and spleen and the diaphragm are usually very firm. The omentum is thickened and rolled up, and its boundaries are lost in the general adhesions. In many cases it is almost impossible to orient the abdominal organs, everything being so densely bound together by adhesions, all free surfaces being covered with a thick yellowish or grayish layer of fibrino-purulent exudate. In the second type the peritoneal surface is covered or strewn with numerous tubercles which are more or less confluent. Caseation is usually advanced to a greater or less extent. In the later stages the entire peritoneum becomes covered with a layer of tuberculous granulation tissue containing caseous centres. Adhesions are not numerous and the peritoneal cavity contains a large amount of serous or sero-fibrinous exudate.

In the chronic fibroid form the peritoneum is thickened and hyaline; adhesions are numerous, but there is little or no fluid exudate. The surface of the thickened peritoneum is usually covered with a fibrinous layer. Circumscribed tubercles may be entirely absent, likewise caseation. The spleen and liver may be covered with a thick hyaline layer, the appearances in general resembling those of hyaloserositis, as mentioned above, or the condition may be mistaken for scirrhus carcinoma. On microscopical examination tubercles are found embedded in the masses of fibroid tissue. These usually contain but few bacilli. In the chronic fibro-caseous form large caseating masses may be found in the adhesions or in the peritoneal surface. The chronic hyperplastic form is characterized by the formation of tumor-like masses of tuberculous granulation tissue. The mesentery may become enormously thickened, and the condition may be mistaken for a new growth. A hyperplastic tuberculosis of the intestinal wall is usually found in association with such cases. Such tumor-like masses are encountered most frequently in the right iliac region. Tuberculous tumor-like masses may also be found in the omentum.

Tuberculous peritonitis occurs at all ages, but is most common in middle adult life. The majority of cases appear to occur in females, although many statistics show a majority of males affected. Children are not infrequently affected. According to Osler the condition, in America, is more frequently found in negroes than in the white race. In the female, tuberculous peritonitis is more frequently associated with tuberculosis of the tubes; in children the infection usually comes from the intestines. The condition not infrequently occurs as a terminal infection in hepatic cirrhosis.

The symptoms of tuberculous peritonitis vary greatly. The condition may be entirely latent, and discovered only by accident. In other cases the symptoms may be so severe as to suggest intestinal obstruction. In many instances the onset is like that of an acute general peritonitis. Other cases still resemble typhoid fever and may be mistaken for this disease. The clinical picture varies to such an extent that no very general description can be given. Ascites is usually present, though the amount of exudate may be small. In the acute cases the abdomen may be distended by tympanites, and meteorism is also of frequent occurrence in the late stages of the adhesive form. Fever is always present, though sometimes light. It may be remittent, intermittent, or continuous, and may reach 103°-104° F. A subnormal temperature is not uncommon in the chronic cases, the temperature for days in some cases running 95°-97° F. The patient may appear well nourished or may be emaciated and cachectic. Gastro-

intestinal disturbances are the rule, and the bowels are either constipated or loose. The skin sometimes shows pigmentation, and the condition may be mistaken for Addison's disease. The two conditions may, however, exist together. In those cases in which the tuberculous peritonitis is secondary to chronic tuberculosis elsewhere the symptoms of the former may be overshadowed by those of the primary affection. An important local sign in tuberculous peritonitis is the presence of tumor-like masses in the abdomen. These may be due to omental thickening, encapsulated exudation, thickening of the intestinal coils, enlargement of the mesenteric glands, caseating masses, nodules of tuberculous granulation tissue, etc. A friction rub may often be felt over the tumors. The omentum is frequently rolled up and thickened, forming a rope-like tumor lying transversely across the abdomen above the level of the umbilicus. In connection with the symptoms this local sign is of great importance in the diagnosis of tuberculous peritonitis.

The disease pursues a varied course. Spontaneous healing may occur. In the severe acute cases death may take place suddenly as in acute general peritonitis not due to tuberculosis. In the chronic cases the patient may gradually become marasmic and die from general weakness. The course of the affection is subject to various complications which may bring about a fatal termination. Obstruction of the intestine from the contraction of adhesions, perforation of the exudate into neighboring organs, fatal hemorrhage, etc., are the most common of these. Death may take place from the primary tuberculosis, or a general miliary tuberculosis may terminate the case. The prognosis in tuberculous peritonitis has, however, been greatly modified by the results of laparotomy.

DIAGNOSIS.—The diagnosis of acute general peritonitis is usually very easy in those cases in which there is a characteristic picture of abdominal tenderness and distention, vomiting, and collapse. The starting-point of the inflammation is often very evident in cases in which a primary condition, such as typhoid fever, gastric ulcer, puerperal infection, etc., has already been recognized. Careful inquiry and search for such a cause should always be made. A history of previous attacks suggesting appendicitis, of pelvic disease, gastric ulcer, etc., aids greatly in establishing the starting-point. Such a cause cannot always be easily determined. Since many cases are first seen only after the tenderness and distention are marked, the physical examination cannot always be as thoroughly carried out as is desirable. In such cases the pelvic organs should be examined thoroughly. In some cases the diagnosis becomes very difficult, since similar symptoms may be produced by other conditions. Acute enterocolitis, acute intestinal obstruction, intestinal ulcers, acute hemorrhagic pancreatitis, ruptured tubal gestation, embolism of the superior mesenteric artery, rupture of an abdominal aneurism, etc., may present the picture of peritonitis so that it may be impossible to say whether the latter condition has been set up or not. A diagnosis of peritonitis may be given under these conditions when no evidences of it can be found at autopsy. The mistake may be easily made in those cases of typhoid fever in which the tympanites, abdominal pain, and constitutional symptoms are very marked. The presence of parasites in the intestinal tract may also give rise to symptoms suggesting peritonitis. In those cases in which the local symptoms are not marked, while the general collapse is severe, the diagnosis may be entirely missed.

The diagnosis of circumscribed peritonitis is almost wholly dependent upon the recognition of the condition from which the inflammation proceeds. This cannot always be accomplished, and it is often necessary to study the case for some time before a diagnosis can be made. The condition is most often mistaken for a tumor. On the other hand, the distended bladder and pregnant uterus have been mistaken for peritonitis. In doubtful cases aspiration of local tumors should always be carried out.

The diagnosis of chronic peritonitis is sometimes very difficult in so far as a differentiation between simple chronic peritonitis and tuberculous peritonitis is concerned. It may be borne in mind, however, that the former condition is very rare. In those cases in which it is a sequela of an acute process the previous history of the case usually clears up the matter, but in those cases in which the disease develops gradually and insidiously the determination of the nature of the process may be very difficult. The patient's family and individual history must be considered, a careful examination of the thorax and genitals must be made, the abdomen aspirated, and the exudate examined. A hemorrhagic exudate favors tuberculosis. Carcinoma may be diagnosed by the finding in the exudate of small bits of tumor tissue or cells containing atypical division figures. The exudate should also be stained for tubercle bacilli, and animal inoculations may be made. The tuberculin test may also be given. The occurrence of pulmonary, pleuritic, or genito-urinary tuberculosis makes it almost certain that the peritoneal condition is likewise tuberculous. In children the symptoms of the condition known as *tabes mesenterica* are chiefly due to the tuberculous peritonitis present. Tuberculous peritonitis is often a terminal event in hepatic cirrhosis.

Blood Examination.—The red cells are usually diminished in all forms of peritonitis, to a slight or moderate degree in acute forms, but in the chronic cases the anemia may be marked. During the acute febrile stage the leucocytes are usually slightly increased. In purulent peritonitis the leucocytosis may be more marked, but sometimes is not present or the leucocytes may even be diminished. In perforative peritonitis the beginning of the inflammation may be marked by a leucocytosis. In typhoid fever perforation may be marked by an increase of the polymorphonuclear leucocytes, or the percentage of these may rise without an increase in the total number, or the leucocytes may not be affected. Likewise in appendicitis a very high leucocytosis is suggestive of a beginning peritonitis. In tuberculous peritonitis without obstruction and secondary infection with pyogenic organisms, the leucocyte count is usually low. As a rule leucocytosis in this disease is a sign of a complication.

Hysterical Peritonitis.—Cases have been reported of hysterical conditions in which all the symptoms of peritonitis were simulated: sudden onset, abdominal distention, pain and tenderness, vomiting, symptoms of collapse, etc. Fever may also be present. The cases usually give a history of recurrent attacks without apparent cause. Other hysterical symptoms may be wanting so that a mistaken diagnosis may easily be made.

TREATMENT.—The treatment of acute peritonitis has been much discussed in recent years, particularly from the operative side, and as a result of improved surgical methods the prognosis in this so frequently fatal condition has been greatly improved. There is much conflicting opinion as to the exact details of the treatment, and various writers even disagree as to more essential points. A survey of the literature, however, seems to indicate that the principle of early surgical interference is gaining ground. As a prophylactic measure in the case of an impending perforation operation has in some quarters met with notable success. With improvement of the surgical technique much may be hoped from the early surgical treatment of cases of acute general peritonitis, and it is not improbable that this disease, at present so dreaded, may be divested of much of its importance.

The older treatment may be summed up as follows: rest, opium or morphine, local applications, hot or cold, local application of leeches, milk diet, ice, small quantities of soda water, etc. In cases of distention the intestines were sometimes tapped with a fine trocar. The intestinal tube was also used to remove gas from the large bowel. Much discussion has also been waged over the use of salines in this condition, some authorities advocating them as an aid to the removal of the exudate,

others condemning such use on the ground of danger in the case of intestinal lesions.

While in general the above outline of treatment is still carried out in many cases, important modifications have been made, and the surgical treatment is coming more and more to the foreground. Mikulicz, Krönlein, Oberst, Wagner, Trever, Péan, and Körte were among the first to advise laparotomy for general peritonitis. Many other writers have recently followed in their lead. The operative treatment in general consists of opening the abdomen, removing the exudate as completely as possible, the so-called "toilet of the peritoneum," and after-drainage. The earlier in the disease, especially in the case of perforative peritonitis, the more likely is the operation to be successful. Authorities differ in their views as to the value of washing out the peritoneal cavity. Some recommend very highly the use of large quantities of sterile physiological salt solution, all parts of the abdomen being thoroughly flushed. This seems a rational proceeding, and from the published reports a number of cases have undoubtedly been saved by it. Appropriate general treatment is of course given, intravenous saline injections being freely used during the after-treatment. In those cases in which adhesions have already formed the washing out of the exudate is more difficult and less perfect. This fact is therefore the chief reason for operating as early in the disease as possible. Mikulicz advises several incisions for the purpose of draining and flushing localized collections of exudate.

On the other hand, Krogus does not advise the flushing out of the cavity, apparently for the reason that he does not think it accomplishes the desired purpose. He recommends the dry absorption of the exudate, all parts of the peritoneal surface being thoroughly mopped with sterile gauze compresses and particular attention being paid to the pelvis and the subphrenic space. In order to render all parts of the peritoneum accessible he makes two incisions through the abdominal wall, one along the lateral border of the right rectus, the other along the lateral border of the left. If the exudate in the pelvis cannot be removed through these openings, he advises a counter-opening in the posterior wall of the fornix vaginae in women, and a parasacral opening in males. After cleansing the peritoneum as perfectly as possible, large Mikulicz iodoform tampons are placed in the pelvis and in the upper and lower portions of the abdominal cavity. These become offensive in a few days and are renewed, the outer dressings being frequently changed. In addition he uses intravenous saline injections, intestinal irrigation, and morphine when necessary. The occurrence of secondary collections of exudate, particularly subphrenic abscess, should be watched for and when found they should be opened and cleansed. Although these principles are applied chiefly to perforative peritonitis occurring in appendicitis they may be utilized in the treatment of all forms of acute general peritonitis.

The surgical treatment is particularly applicable to local circumscribed peritonitis. The encapsulated exudate should be evacuated by incision or puncture, and the cavity washed and treated as a chronic abscess cavity. The details concerning drainage, packing, after-treatment, etc., must be left to the judgment of the operator.

In the case of subphrenic abscess an incision may be made at the edge of the ribs, or the transpleural route may be followed by resecting several ribs. In the chronic forms with multiple adhesions relatively little can be expected from operative procedures.

In the case of tuberculous peritonitis laparotomy is at present the only method of treatment offering hope of improvement or cure, and is universally advised for this condition. The fact that a tuberculous peritonitis may spontaneously heal after laparotomy was accidentally discovered by Spencer Wells in 1862. So much has been written upon this subject that the reader is referred to some one of the recent monographs relating to it. The relation between the laparotomy and the cure of the tuberculosis is wholly unknown, although numerous theories—effects of daylight, evaporation, irritation of

the peritoneal surface, promotion of healthy granulation-tissue formation, increase of the peritoneal resistance, hyperleucocytosis, increased bactericidal action of the exudate, etc.—have been advanced in explanation. Surgeons differ very much in the details of technique in their operations upon such cases. Some open the abdomen and remove the exudate with dry sponges; others flush with warm physiological salt solution; others still wash out the cavity with solutions of salicylic acid, etc. There is also a difference of method in regard to the removal of the organs (tubes, lymph glands, etc.) primarily affected. In general it may be stated that laparotomy is indicated in all cases of tuberculous peritonitis in which the general condition of the patient permits, or in which there is no evidence of cerebral, pulmonary, or extensive glandular or bone tuberculosis. The medicinal treatment of tuberculous peritonitis is advised in some cases, the administration of iodoform as well as its use by inunction having been reported as resulting in cures. Cases of cure have also been reported as following the use of tuberculin.

Very recently a number of writers have been advising conservatism in the treatment of acute general peritonitis by operation. Those who advocate a medicinal method modify the older methods by giving no food by the mouth, employing rectal feeding, allowing no ice, checking thirst by wet gauze to lips and by rectal injections, giving no cathartics, administering small doses of morphine, and applying continued cold to the abdomen. This treatment is based upon the theory that the peritoneal exudate itself may weaken the virulence of or destroy the germs gaining entrance to the cavity. Alcohol has been strongly advised in the treatment of puerperal peritonitis, large and frequent doses being given.

The injection of purgatives directly into the intestinal canal has been advised and as strongly condemned.

Some surgeons advise against operation in sthenic cases of perforative peritonitis without symptoms of sepsis, on the ground that spontaneous resolution may occur. There is, however, a great danger that such cases may under the influence of morphine be allowed to drift along until too late.

Hot vaginal douches have been strongly recommended in cases of pelvic peritonitis. If the external genitals are protected injections of water at 40° C. may be given without discomfort. The pelvis should be elevated, and about 4-5 litres of water used for the irrigation daily. Tampons of glycerin or potassium iodide with glycerin are applied after the irrigation. Stratz in particular claims good results from the application of this method in pelvic peritonitis associated with pyosalpinx.

The statistics of the results of the treatment of acute general peritonitis by operation are very encouraging. Krogus in his monograph published in 1901 has made an elaborate study of the results of operation in general peritonitis following appendicitis. The percentage of cures ranged from 28.5 to 46.

Surgical interference in the case of impending perforation of gastric or intestinal ulcers, appendicitis, rupture of sac in ectopic gestation, salpingitis, necrotic ovarian cystomata or subserous uterine fibromata, hemorrhagic pancreatitis, etc., has proved of the very greatest value as a prophylactic measure. With improved methods of diagnosis much may be hoped for by the further development of such prophylactic operations.

The literature of peritonitis is enormous. Collections of bibliography will be found in the article by Döderlein in Veit's "Handbuch der Gynäkologie," and in the one by Eichhorst in Eulenburg's "Real-Encyclopädie." An exhaustive review of the literature of peritonitis from the year 1885 to 1900 is given by von Bruns (*Cent. f. allg. path. Anat.*, 1901.) *Aldred Scott Warthin.*

PHYSICIAN, RELATION OF, TO THE LAW.—In this we have a subject of much interest and importance, yet one that is too little known among the profession at large. Experience, while a valuable teacher, is, where the law is concerned, a very expensive one; so it is the

duty of every practitioner to familiarize himself with the laws having a medical aspect, remembering that local, not national, statutes prevail.

In several States medical jurisprudence is one of the subjects of examination as conducted by the State Board of Examination and Registration, and is given equal importance with the other branches, as it should be, for there is no more pitiful sight than to see a medical witness, bright in other subjects, held up to ridicule by attorneys because of ignorance of the legal requirements of the particular case in question.

Judges throughout the Union try to sustain the same rulings along general lines, but it is impossible to lay down fixed rules for all sections of the country in an article of this nature, as the wording of the statutes differs in almost every State; hence they are capable of various interpretations.

License to Practise.—In many of the States good laws have been enacted requiring that the applicant for license present a diploma from a recognized school, showing the necessary training to qualify him for the work which he desires to undertake. Some States, in addition to the presentation of a diploma, require an examination before a State or local board, and will admit no one to the practice of medicine and surgery until a certificate of qualification is issued to the applicant by the Board of Examiners.

After the applicant has received the necessary State documents it is his duty to present the same and his diploma for record to the clerk of the county in which he desires to locate. In case of removal from one county to another the papers must be again recorded in the office of the county clerk. The law must be complied with in every particular, else non-recognition will result if he should be called into court.

If one is located near a county or State line, cases can be attended in the adjoining county or State without a record in the same, provided the practitioner be legally recognized in the county and State in which he is located.

In case of change of location to another State all the local laws must be investigated and fully complied with, the physician going before examining boards if necessary.

As a measure cannot be made retroactive, those who have qualified under former acts are entitled to all the rights and benefits of the law existing at the time of their qualification. In many of our Western and Southern States are to be found legal practitioners who received their medical training as members of a hospital corps during the civil war, or as apprentices of physicians who established themselves in a legal way under the very lax laws that formerly covered the practice of medicine in these localities. Many of these men, being keen observers, and having had the advantages of short post-graduate courses, do much good.

Different Schools.—Under the law the members of the different schools have equal rights. Each is allowed to practise the method in which he has been trained, and he can recover by law such fees as he can prove that he has earned, even if men of other schools testify that the treatment given was not all that it should have been. Decisions have been rendered in several States granting freedom of practice to osteopaths when it was fully demonstrated that their principles in the handling of infectious and malignant cases were faulty.

Malpractice.—In order to recover in a malpractice suit it is necessary to prove that the attending physician or surgeon did not use or display ordinary skill in handling the case in question. This ruling gives a wide latitude in arriving at what constitutes "ordinary skill." A city practitioner, with vast opportunities in hospital work, is expected to have greater skill than the man in country practice whose opportunities are necessarily limited.

A recent ruling of the Superior Court of Cincinnati set aside a judgment rendered in favor of the plaintiff by a lower court, on the ground that expert testimony had not been introduced to show that the attending physician had failed to use or display ordinary skill and care in the

handling of this particular case. This ruling is most wise and will no doubt be the cause of much less annoyance, to say nothing of loss of time and money, to the profession generally, as unscrupulous attorneys have in recent years been filing suits against physicians who were fortunate enough to possess funds or property, in the hope of blackmailing by a so-called compromise, realizing that the majority of men would rather pay them a fee than stand suit under the older rulings.

Like others under the law the physician is liable for damages if he is careless and neglectful in his work. When he is employed to treat a case the contract is implied, and the person or persons employing the medical man are to understand, when the case is accepted, that ordinary skill is to be shown.

Suggestive Therapeutics.—This subject, which has attracted considerable attention in recent years, is one that has its legal complications if carried too far.

A Cincinnati physician was recently indicted on the charge of obtaining money under false pretense as a result of erroneous ideas as to the scope of this line of treatment. A woman who had been under the care of a number of physicians for some time, going first to one and then to another, decided to make another change and called in the man in question. After going into her history, perhaps realizing that his predecessors had done all that was possible in a strictly medical way, he decided that hers was a good case for suggestion, and to this end informed her that she had a tumor which it would be necessary for him to remove. The patient consented and was removed to a hospital for the operation. As an endometritis existed, the womb was curetted, and, after the effects of the anæsthetic had disappeared, the patient was informed that the operation was successful. The attending physician reported that the recovery was rapid, and that the patient had fully recovered from all pre-existing symptoms. After a time the patient asked to be shown the tumor which had been removed. Several excuses were offered, but the patient was persistent; so, to continue the suggestion, the woman was shown a piece of beef so arranged as to resemble a tumor. In some manner it was suggested that a section be made and studied by a pathologist to ascertain the nature of the growth. This suggestion was acted upon and the "tumor" was sent to a well-known man for examination and report, with the result that criminal proceedings were begun against the too ardent advocate of suggestion.

In all cases in which suggestion is likely to benefit, members of the family should be consulted and their consent and co-operation obtained. If actual deception is considered necessary a consultation should be arranged, all the facts bearing on the case reduced to writing, and the document signed by the attending physician, the consultant, and some responsible member of the family, and then carefully filed for reference.

In all cases of suggestion the charges made for service rendered must be in accordance with the work actually performed, else fraud will be claimed and established.

Cases Having a Legal Aspect.—All cases of this nature should be considered in every possible detail, and full notes should immediately be made and recorded in a permanent form for future references. A judge is always of the opinion that a doctor should notice everything, and if he fails in his examination on the witness stand, the public is ready to censure him and the opposing attorneys make light of his ability in their arguments.

If a physician is called to see an individual dying as the result of accident, assault, or attempt at self-destruction, who is capable of making an ante-mortem statement, he should insist that the latter be reduced to writing, signed and witnessed. Before his statement is taken the patient must be informed that death is certain to follow, as dying declarations are of great legal importance, and this point must always be made. The simple statement of an injured person who may be of the opinion that recovery will follow, is of very little value.

When viewing a dead body the physician should note

its position, not alone as regards the relation of its members and the surface on which it lies, but also as regards its relation to all surrounding objects. Very careful inspection must be made of the surface of the body and of all wounds, scars, marks, livid spots, and other abnormal conditions; they should be measured and the results should be recorded, together with exact descriptions and a statement of their anatomical relations.

As rigor mortis is of value in determining the state of health at the time of death, this feature must not be overlooked. A note must also be made in regard to the following: Whether the surface of the body is livid or pallid, what expression the face bears; whether the body is warm or cold, as revealed by the temperature of the mouth or the axilla; the exact time at which the body was seen; the condition and nature of the clothing; the contents of the pockets; whether there was any jewelry; at what time—giving hour and place—the person was last seen alive, and whether he or she was alone; if vomited matter is present, collect some of it for chemical analysis; note the presence or absence of weapons, drugs, bottles, or other possible clues.

If a post-mortem examination is necessary to establish the cause of death, every vital organ should be thoroughly examined. The stomach and intestines should be examined for inflammation, and if such areas are found the exact seat and possible nature must be determined. The contents should be collected for examination. The amount, odor, color, and other characteristics are to be noted. If death by poisoning is suspected, the stomach, liver, intestines, and kidneys should be removed for a chemical examination. All vessels used for the collection of vomit, or of other fluids and organs removed, must be known to be perfectly clean and not to have been where contamination with arsenic, strychnine, or mercury could have been possible. Note whether the rectum is empty or filled with feces; the latter condition indicating that purging could not have taken place. Carefully examine the lips, mouth, pharynx, larynx, œsophagus, and trachea for evidences of the corrosive action of poison.

Note whether there is an abnormal amount of fluid in the pleural cavity, pericardium, cranium, or spinal canal. Thoroughly investigate the action of the valves of the heart.

In cases in which death has resulted from the slow action of poison it is important to investigate the changes which may have taken place in the kidneys and liver. In all cases of death from an unknown cause the best way of arriving at a definite conclusion as to whether death was due to natural or to violent means is by the slow process of exclusion. Full notes along this line will make the position of the medical witness secure, as he is then prepared to meet the attack of attorneys when by cross-examination they try to make the point that death could have resulted from other causes.

When the medical man is called upon to make an examination of a body that has been buried, it is necessary that the body be identified by some one who can positively state that the body in question is the one ordered examined, else the point will be made and sustained that it is possible that the wrong body was exhumed.

Criminal Assault.—This is a subject often brought to the attention of the medical witness, especially in the case of children below the age of ten. Nona pudendi, when discovered by those in charge, is often thought to be the result of an assault, and the afflicted child, not understanding the true nature of the questions asked, will make admissions that result in serious charges being preferred against an innocent person. The other extreme is to be considered at all times in connection with assault, as in rare cases only the most careful examination will reveal physical signs; for wounds and abrasions of the hymen and vagina heal rapidly.

Casper¹ reports a case in which, on examination eleven days after the assault, no signs of the outrage could be observed.

The leucorrhœa common in childhood is often the cause of rape charges. Children of a scrofulous habit

may present points of ulceration about the vagina and vulva, accompanied by a purulent vaginal discharge, so that in any case the presence or absence of gonococci must first be determined and deductions made accordingly.

A child, as a rule, makes little or no resistance at the time of assault; so the bruises and other marks of violence usually observed in older females are absent and the case resolves itself into ascertaining the cause of abnormal conditions about the genital tract.

As false charges are sometimes preferred by older females, it should always be the rule to look upon all cases from this point of view when beginning the examination. If marks of violence are shown, ascertain the time of the alleged assault, and observe whether the wounds or bruises are older than the time indicated; also obtain all the facts as to the manner of the assault, and note whether the marks of violence presented could have resulted in the manner described.

When an examination of the genital tract is made it must be remembered that the hymen is at times destroyed as the result of a purulent discharge, and also that, in some women, it is destroyed at the beginning of the menstrual period. On the other hand, the presence of an intact hymen is not a positive sign that penetration has not taken place. The important thing, in such cases, is to determine whether or not the vaginal canal has been dilated.

In the event of assault on a married woman, or on one who is not a virgin, evidences of injury to the genital tract may or may not exist. If the assailant is alone in his deed, marks of violence are always to be found about the person of the victim, often including the vulva and vagina, for the resistance offered causes undue force to be used in penetrating. If the assailant, however, has assistance, either manual or in the form of drugs, no signs of assault may be present. Where drugs have been administered, their character must be discovered, if possible, and their physiological action fully investigated, in order that it may be shown that hallucinations have not led to the making of the charge. The hallucinations produced by the administration of anesthetics for slight operations have resulted in dentists being accused of rape.

A case of extreme interest is that of a young woman who was violated while asleep. She had returned from a long walk with her accepted admirer, had drunk a glass of ale, then had fallen asleep in his presence, and the assault followed. Owing to the fact that she was an unusually heavy sleeper, the pain produced by laceration of the hymen and distention of the parts had not been sufficient to awaken her. An examination by a competent medical man revealed the usual physical signs of recent defloration, and the assailant admitted his guilt when charged with the crime.

The medical witness is usually concerned in cases of young children and the feeble-minded; the testimony of the victim commonly establishing the charge in adult cases.

Criminal Abortion.—While we, as a rule, divide the expulsion of the fœtus before the normal termination of intra-uterine life into abortion, miscarriage, and premature delivery, the law regards all under the one head.

It is the duty of the medical witness to distinguish between natural and violent abortion, and, if the cause be violence, to ascertain whether it was criminal or accidental in character. Criminal abortion may be produced by mechanical means or by the use of drugs acting upon the uterus. When mechanical means are used, marks of the violence can usually be demonstrated on the mother and on the expelled fœtus, unless the work has been done by one thoroughly familiar with the anatomy of the parts, and who exercises great care when he introduces the instrument for the purpose of rupturing the membranes.

The use of medicinal substances, by profoundly shocking the system and in this indirect way affecting the uterus, at times produces abortion. When seen the pa-

tient is usually giddy, nauseated, and purging. Drugs, even ergot, can be expected to cause an evacuation of the uterus only after the third month of gestation, the muscle fibres not being well enough developed prior to this time to respond; in fact, it is rare that the effect can be obtained until the fifth month of pregnancy is reached.

The diagnosis, shortly after evacuation, is rendered easy by a careful examination, which should always be made, as cases of feigned abortion are on record and similar ones will no doubt occur again.

When a physician is called to see a case in which the evacuation of the uterus seems imperative, he should request a consultation, and a full and complete history should be obtained and reduced to writing, if abortion is decided upon.

Infanticide.—By this term we mean the murder of a new-born child. In perhaps no class of cases is the medical expert so handicapped as in this. Many children die shortly after birth, yet live long enough for well-known evidences of this fact to exist, and the question to be determined is whether death was due to natural causes or to violence. Marks of injury may show on almost any part of the body of the infant and be due to forces acting at the time of delivery. The first question that presents itself when one views a dead infant, is what is its age; and in this connection it must be remembered that the younger in uterine age the infant is, the greater the danger of death at birth or shortly after.

The child should be weighed and measured and all details in regard to its degree of development should be recorded, especial care being taken to note the size of the head as compared with that of the trunk, the degree of ossification, the color and thickness of the skin, and whether the surface of the brain is smooth or already presents convolutions. If the child is fully developed it must be determined whether it lived to breathe and whether it was born alive; for, it must be remembered, a child may breathe and yet be born dead. Experiments have taught us that in a still-born child the forcing of air into its lungs in an attempt at resuscitation will produce the same condition as that of a child who was born alive but breathed only feebly. It is only after all these details have been most carefully observed that the physician may feel warranted in forming a trustworthy opinion. In atelectasis the child may be born alive and exist for some hours, yet the lungs will sink in water, even when divided into small portions.

In those infants who have lived long enough to feed, the presence of food or other foreign substances in the stomach proves that the child was alive at birth, and if death is the result of poisoning, the appearance of the gastric mucous membrane or the usual chemical analysis will reveal the cause of death. It must be remembered, however, that it is possible for an infant, still-born, to have amniotic fluid or other contents of the parturient canal in its stomach as the result of an effort to breathe, the material having been drawn into the mouth during such effort and then swallowed before death ensued.

Death from suffocation is very common in the new-born; it may be due to some malformation, to weakness, to the blocking of the air passages with mucus or other substances, or to the effects of too heavy covering. Where destruction is intended and a damp cloth or other impermeable material is placed over the mouth and nostrils, death will result; and if the act has been done without the employment of undue pressure, the medical witness will be at a loss to state whether the child was born alive or dead, his opinion being possibly in favor of the latter view.

Birth Records.—The medical attendant should write down at the time the exact date and hour of birth, the sex of the child, the state of its development and all characteristic marks, and he should place this record on file for reference. In many legal battles such a record has been of value in determining the right of inheritance and has aided in dealing justice where fraud has been attempted. Male children have been substituted for female, living children for those born dead, and a perfect

child for a monster who would not be recognized as a legal heir.

Insanity.—Under this heading we shall not consider those cases in which the insanity is marked by hallucinations and impairment of all functions, but preferably those in which only a careful study will enable the medical witness to determine whether the patient in question is or is not sane, and those who are feigning insanity.

No definite law can be laid down as to what constitutes insanity; all symptoms must therefore be carefully studied and deductions drawn from them for the benefit of the court.

Persons displaying unnecessary hatred to those about them are often presented for examination as to their sanity, as this characteristic is offered in evidence in case of criminal proceedings against them; but unless it can be shown that there is some impairment of the faculties of attention, comparison, and volition, the individual cannot be adjudged insane. The faculties should be examined when the patient is not conscious of the object of the visit made. Ordinary subjects of general conversation should be used in this examination and mental note made of any and all irregularities, which can be reduced to writing as soon as possible after the examination is concluded. During the examining visit some subject should be introduced which requires that the patient shall write a letter of his own composition which, in genuine cases of insanity, will give evidence of the condition that can readily be demonstrated. Patients of this nature should be repeatedly examined, as many of them present lucid intervals.

Perhaps the most common condition in which the average practitioner is called to testify is that of setting aside a will, the charge usually being made that at the time of execution, or possibly of alteration, the patient was not of sound mind. When attending a case in what appears to be the last illness, the physician should note carefully the patient's mental condition from visit to visit, and he should preserve a record of these observations, in order that he may be able, if called as a witness, to state whether the supposed irregularities were due to a weakened mental condition or to an eccentric disposition.

In the case of criminals for whom is entered a plea of insanity, a careful study of their history and the facts and conditions of the crime committed will usually clear up the medical aspect and enable the physician, when on the witness stand, to be sure of his ground.

A sane person will be found to have a motive for the crime, be it plunder or revenge; he is often assisted in the crime and will at first usually deny guilt, except in cases in which the motive for the crime is notoriety, as in the assassinations of Presidents Garfield and McKinley. An insane person will have no motive, or only a fancied one, for the commission of the crime, and, instead of one victim, as would be the case if the murderer were a sane person, he will often kill several, perhaps those most near and dear, and will make no attempt to cover up his tracks or deny the act.

Life Insurance.—Where life insurance is concerned, the medical witness is of importance in determining—for the satisfaction of the heirs of the deceased, of the company carrying the liability, and of the court, if legal action has been started—as to whether death was the result of natural or of violent means. In the case of a natural death it is important to learn how long the individual had suffered from the disease that caused death, and whether or not there were predisposing chronic pathological conditions existing prior to the issuance of the policy covering the case involved. On the other hand, if death resulted from violence, it is necessary to ascertain whether the cause was criminal, accidental, or suicidal.

Accident insurance having now become an extensive business the attention of the profession is frequently called to cases that require the utmost care in arriving at a definite opinion. Diabetic ulcerations are stated to be the result of trauma (a wound received in a barroom fight or an injury caused by a fall)¹ or a syphilitic ulcer-

ation is claimed to be the result of a burn, and so on through the entire list of diseased conditions that produce lesions which can be charged to an accident.

Shrewd criminals often conceive unique plans for defrauding insurance companies, and the medical witness must always be on the alert for such surprises. Post-mortem examinations should always be insisted upon when a case is not absolutely clear.

Partnership.—Agreements are often entered into by members of the medical profession for mutual benefit and a firm name selected. The basis for settlement is decided upon and division made accordingly, but no legal responsibility is assumed by one for the other, and each member of the firm is alone responsible for errors made in his professional work. Should the firm enter jointly into outside investments, they then become liable under the law to the same extent as do the regular commercial unions.

Fees.—The question of fees has ever been a hard one for the medical profession. The courts have ruled that no one is so good a judge as to the number of visits necessary to be made in a given case as the medical attendant, and he can so render an account. In several States fee bills have been enacted regulating the maximum amount to be charged for certain classes of work. As nearly every case—especially those wherein the amount of the bill rendered is claimed to be exorbitant—possesses certain complications, it is not hard for expert opinion to prove to the court or jury that the fee charged is not excessive. By far the most common question that arises in this connection is not the amount, but who shall pay the fee. A prominent Cincinnati surgeon recently sued a corporation for services rendered an employee and lost his case, the court ruling that the defence had proven that the individual who employed the doctor, although he was connected with their concern, had no authority to make contracts, and was simply acting as a messenger for the injured person, and that the patient must be looked to for liquidation of the account.

When answering calls where it is probable that the individual requiring the service will be unable to pay for the same, the physician should ask some one in authority to become responsible. It is not sufficient for a person in authority simply to ask the medical man to assume charge of a case, he must also agree to settle for the service rendered; otherwise liability can be denied and this defence will be sustained by the court. In nearly all sections of the United States this ruling has prevailed where medical men have been called to attend an injured passenger or employee by local agents, conductors, and other minor officials of railway companies. The same ruling applies in cases in which parents have requested attendance upon their children of legal age; the patient being considered liable while the parent is looked upon as a simple messenger without liability. In the case of the wife, legally absent from home, the husband is held to be responsible for medical attention rendered; if, on the other hand, she is not legally absent, she alone is considered responsible.

Consent of Patient.—In cases of injury, or in those in which it has been determined that an operation is necessary, it should always be the rule to obtain the consent of the patient to do whatever is necessary after administration of the anæsthetic. In case the patient is not in a condition to understand, or if the patient is a minor, then the consent of a responsible member of the family or guardian should be obtained. Occasionally one meets with cases in which the individual claims to prefer death to the loss of a limb, and if he still persists in this view after all the facts are set forth, his wish must be respected. It is needless to say that every avenue for a malpractice attack must be carefully guarded either by securing in advance reliable disinterested witnesses or by resigning the case if another practitioner can be found who is willing to assume charge.

Consent procured by misrepresentation has no standing in law.

Mr. Benjamin Vaughan Abbott, in his excellent article

on this subject in the first edition of the *HANDBOOK*, cites a case of much interest, as follows: "A lady became suspicious that a housemaid in her employ had become pregnant, taxed her with it, and gave her notice of dismissal. She denied it. The lady sent for her family physician and ordered the girl to go to her room and submit to an examination. The girl protested, but went to the room followed by the physician. She objected to each of the doctor's requirements, as to removing her clothing, etc. However, she obeyed, remonstrating all the while, and the usual examination was made, resulting in the doctor being satisfied that the charge was groundless. But the mistress dismissed her, notwithstanding. A lawsuit was brought on behalf of the girl against the physician, for damages for assault. The case was several times discussed in court, with the final result in the physician's favor. The courts considered that although the girl remonstrated, yet as she went to her room, undressed, and lay down to be examined, all without being forced, the examination did not take place in a legal sense without her consent. It was a case of reluctant obedience to arbitrary, wrongful command, as distinguished from a forcible compulsion which she was powerless to resist."

Emergencies.—While there is no definite law covering the rights of the profession at large in emergencies, the courts would no doubt sustain any action necessary for the well-being and safety of the public. Health officers are given a wide latitude in all matters of public hygiene and safety and should always be appealed to if possible.

Relation of Physician and Patient.—The relation of patient and physician is acknowledged by law to be most intimate. Any abuse of this confidence on the part of the physician would in all probability render him liable in a suit for damages. Abbott² reports a case from the Michigan courts in which a physician was assessed damages for allowing a non-medical man to be present and render slight assistance at an obstetrical case, notwithstanding the fact that the physician showed that circumstances required his being accompanied by the man in question, and that there was no other protection from the prevailing storm than the room in which the woman was confined.

In damage suits the ruling has been made that the attending physician may testify as to what the patient said regarding the manner in which the accident occurred, it being held that the law in its strict sense refers to those things necessary for the physician to know regarding family history, habits, etc., for the proper treatment of the case, and not to voluntary admissions made during the visit. This ruling would not hold in criminal cases if the patient should admit that a wound had been received while doing a dishonest act. Here the ruling has been made that this is imparted in confidence and must not be revealed under any circumstances. On the other hand, the law will not protect a third party, guilty of crime, but will allow the testimony of the attending physician to assist in conviction. To illustrate, we will consider the case of a young woman dying as a result of criminal abortion. Here all the facts were given the attending physician as a dying statement. This was admissible as evidence to aid in the conviction of those responsible for her condition. In the case of *State vs. Pierson*, the latter was charged with having caused the death of one Withey by the administration of arsenic. In this case the physician who attended Withey in his last illness was allowed to testify as to what he saw and heard. This was sustained by the Court of Appeals under the ruling that the law was to protect the patient and physician in legitimate communications, not to shield criminals.

Wills.—It is not often that the physician is concerned in the drawing of such documents, and it should be avoided if possible, especially if complicated details are to be arranged or the doctor is to be a beneficiary. In cases of emergency it may be necessary for the attending physician to draw up the will, in which case any simple, but clear, form will be sufficient. Have the instrument

signed and witnessed by three or more competent individuals and deliver the document into safe hands.

Mark A. Brown.

¹ Taylor's Medical Jurisprudence.

² Abbott: REFERENCE HANDBOOK OF THE MEDICAL SCIENCES, Vol. V., page 673, first edition.

PHYSICIANS: RELATIVE NUMBER AS COMPARED WITH EXISTING POPULATIONS.—The relative number of physicians in any country or population depends upon many circumstances and conditions, such as the laws governing the practice of medicine, the progress of medical education, the prevalence of empiricism, and many other social conditions.

In some countries the number may be ascertained from the figures of the census; in others, as in Germany, from careful enumerations of the medical profession made by the Government.

In the United States at the present time certain medical directories, issued at frequent intervals, contain this information, with an approximate degree of accuracy.

The following tables present the numbers of physicians per 10,000 of the population in each of the United States in the two years 1898 and 1902:

RATIO OF PHYSICIANS TO THE POPULATION IN THE UNITED STATES IN 1898 AND IN 1902 IN GROUPS.

States and Territories.	Ratio of physicians to the population, 1898.	States and Territories.	Ratio of physicians to the population, 1902.
California	23.8	California	26.1
Iowa	23.7	Colorado	23.4
Indiana	21.4	Vermont	21.5
Vermont	20.8	Indian Territory	20.7
Ohio	20.3	Oklahoma	20.6
Illinois	19.3	Missouri	20.3
Arizona	19.1	Ohio	20.3
Missouri	19.0	Arkansas	19.7
Colorado	18.7	Indiana	19.7
Tennessee	18.6	Maine	18.8
Massachusetts	18.5	Iowa	18.4
New Hampshire	18.1	Kansas	18.4
Maryland	17.9	Illinois	18.3
New York	17.7	Tennessee	18.2
Texas	17.5	Maryland	18.1
Arkansas	17.2	New Hampshire	17.8
Maine	16.8	Michigan	17.6
Kentucky	16.5	Massachusetts	17.2
Nevada	16.3	Texas	17.2
Michigan	16.0	New York	16.9
UNITED STATES	15.4	Kentucky	16.3
Connecticut	15.2	Nevada	16.3
Rhode Island	15.2	UNITED STATES	15.9
Oregon	14.9	Pennsylvania	15.4
West Virginia	14.9	Oregon	15.3
Pennsylvania	14.9	Rhode Island	15.2
Oklahoma	14.4	West Virginia	15.1
Florida	14.4	Connecticut	15.0
Delaware	14.2	Washington	14.9
Montana	14.0	Delaware	14.7
Idaho	13.8	Arizona	14.5
Kansas	13.6	Nebraska	14.3
Virginia	12.3	Georgia	14.2
Georgia	12.3	Idaho	13.4
New Jersey	12.1	Montana	13.2
Alabama	11.9	Florida	13.1
Washington	11.3	Wyoming	13.0
Wisconsin	11.3	Alabama	12.2
Louisiana	11.0	New Jersey	12.1
Mississippi	10.9	South Dakota	12.1
Utah	10.2	Virginia	12.0
Minnesota	9.6	Wisconsin	11.5
Wyoming	9.4	Utah	10.7
Nebraska	9.2	Alaska	10.7
South Carolina	8.7	Minnesota	10.6
North Carolina	8.5	Louisiana	10.6
North Dakota	7.8	Mississippi	10.1
South Dakota	7.7	North Dakota	9.3
New Mexico	7.2	New Mexico	8.5
		North Carolina	8.2
		South Carolina	8.1

Allowance has been made in the foregoing tables for increase of population.

Examination of the foregoing table shows that the ratio of physicians in the United States has increased from 15.4 per 10,000 inhabitants in 1898 to 15.9 in 1902.

The ratio had increased in each of 29 States and Territories, and had decreased in 19. Alaska and the Indian Territory are included in the second list, but not in the first.

The States in which either the increase or decrease appears to have been excessive are Iowa and Arizona, with decrease of 22 and 24 per cent. respectively, and Kansas, Wyoming, Oklahoma, Nebraska, and South Dakota with increase of 35, 38, 43, 55, and 57 per cent. respectively.

The map or chart shown herewith was constructed for the year 1898 and presents the ratio of physicians to the population by means of different shadings, black indicating the highest ratio.

The information obtained from these figures must be deemed to be only approximately accurate, since the two essential factors, namely, the directory list of physicians and the census enumeration of the population, with the necessary estimates for intercensal years, cannot be regarded as strictly correct in a rapidly growing country like the United States, subject to the constant change which attends the migration of population, not only from foreign countries to the United States, but also from one State to another.

In general, however, the figures for the larger States, and for the New England, Middle, and Southern States, embraced in all the groups except the first, may be considered to be fairly trustworthy.

and in Porto Rico and the Philippines less than 1 per 10,000.

The relative number of physicians in other countries is generally less than it is in the United States. Prinzing* published the following figures in 1901 for the principal European countries:

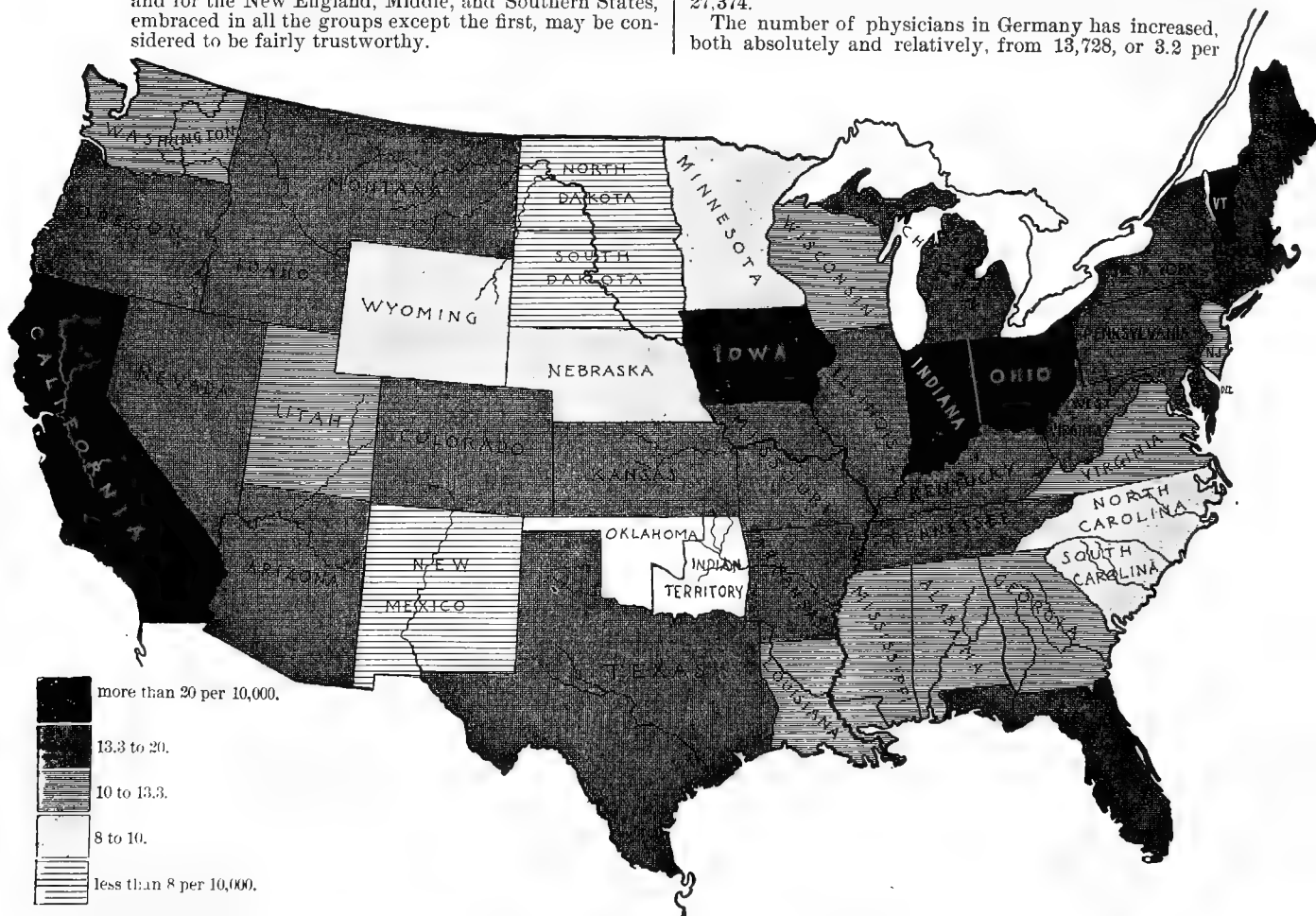
Number of physicians and surgeons to each 10,000 inhabitants: In Germany, 5.1; in Austria, 4.1; in Hungary, 2.8; in Italy, 6.3; in Switzerland, 6.1; in France, 3.9; in Spain, 7.1; in Belgium, 5.2; in England, 6.1; in Scotland, 7.7; in Ireland, 5.6; in Denmark, 6.4; in Norway, 5.3; in Sweden, 2.7; in Russia (European), 2.7.

The number of homœopathic physicians in the principal states of the German Empire were as follows:

In Württemberg 30 or 3.7 per cent. of the whole number of physicians.
In Russia 136 or 0.9 of one per cent. of the whole number.
In Baden 8 or 0.9 of one per cent. of the whole number.
In Saxony 15 or 0.8 of one per cent. of the whole number.
In Bavaria 16 or 0.6 of one per cent. of the whole number.

At the last enumeration of physicians in the German Empire, the whole number of homœopathic physicians in the empire was stated to be 240, or less than 1 per cent. of the whole number of practitioners, which was 27,374.

The number of physicians in Germany has increased, both absolutely and relatively, from 13,728, or 3.2 per



Number of Inhabitants to Each Registered Physician.

FIG. 5193.—Ratio of Physicians to the Population in the United States, per 10,000 Inhabitants in 1898.

The figures for the Philippine Islands, Hawaii, and Porto Rico are not given in the table, since they can hardly be regarded as valuable for purposes of comparison. The ratio in Hawaii is stated to be 5 per 10,000,

10,000 inhabitants in 1876, to 27,374, or 5.1 per 10,000, in 1900.†

* Zeitschr. f. Socialwissenschaft., 1901, Bd. 4, Hft. 7.
† Rheinischer Kurier, 1901, No. 415.

In the whole of Prussia there were registered in 1900 16,100 physicians, 956 dentists, and 3,118 apothecaries.*

Prinzing also states that quackery has gained so strong a foothold in Germany as to demand energetic measures for its suppression. Weavers, barbers, shoemakers, and persons of other ordinary occupations are often found practising as physicians.

The relative number of quacks in 1898 in the principal German states were as follows: In Saxony, 16.4 per 10,000; in Württemberg, 5.5; in Prussia, 5.3; in Bavaria, 4.5; in Baden, 2.9; in Hesse, 2.9; in Alsace-Lorraine, 1.3.

The veterinary surgeons in Germany at the last enumeration were 3,813 in number, and when compared with the class of patients whose ills they are called upon to relieve, were found to be in the proportion of 1 to every 1,240 horses and every 5,677 head of cattle.

The proportion of physicians in the cities is, as might be expected, much greater than that of the rural districts. For example in Germany in 1876, in the cities and towns having more than 5,000 inhabitants in each, the ratio of physicians was 7.5 to each 10,000 inhabitants, and in the rural districts only 1.8 per 10,000. These figures had increased respectively to 8.4 and 2.4 in 1898.†

The ratios of physicians in the great cities of Europe and the United States were as follows during the years named: London (1895), 12.8 per 10,000 population; Paris (1896), 9.7; Berlin (1900) 14.1; Vienna (1896), 13.0; Brussels (1897), 14.7; Budapest (1896), 16.4; Madrid (1899), 24.4; New York (1901), 17.1; Chicago (1901), 20.5; Philadelphia (1901), 21.8; St. Louis, 26.3; Boston, 26.8; Baltimore, 23; Cleveland, 21.9; Buffalo, 19.6; San Francisco, 31.5. Samuel W. Abbott.

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PITYRIASIS ROSEA.—Pityriasis rosea is a disease of the skin characterized by the development of symmetrically distributed patches, roundish or circinate in outline, slightly scaly and of a faint red color. It is one of the rarer dermatoses. The disease has been described under several names. Pityriasis rosea, the name given it by Gibert, is the one nearly universally used now. It was described by Hebra under the name herpes tonsurans maculosus, and by Bazin under the title pityriasis maculata et circinata.

SYMPTOMATOLOGY.—The eruption occurs in two forms, the macular and the circinate. Probably the first lesion in both forms is a very small pinkish macule or papule which rapidly spreads to form the characteristic macule or patch of the disease. In the macular type the lesions are roundish patches, gradually fading into the healthy skin, of a pinkish color and covered with fine branny scales. These patches vary in size from one-sixteenth to three-quarters of an inch in diameter, and are of a reddish to fawn color. Frequently the periphery of the lesions will show the erythematous color while the centre will be fading.

The circinate type of the disease differs from the macular in that the tendency of the patches to spread peripherally is more marked. In this form the border spreads while the centre fades. The typical lesion of this form, therefore, is a more or less circular patch with a pinkish border and a fawn-colored scaly centre. Adjacent patches of this sort may coalesce and thus form peculiar gyrate figures. These patches do not usually become larger than an inch in diameter. By the time they reach that size the reddish border breaks up and

fades out, leaving the characteristic fawn-colored stains of the disease. The lesions are apt to occur in successive crops, so that it is possible to see at one time the minute papules of the beginning of the disease, along with the patches and circinate figures of a later stage of the process. At times the eruption remains papular for the most part throughout its entire course, only a few patches or circinate figures developing.

Brocq called attention to the fact that a single primary patch, usually of large size and situated upon the abdomen, preceded by ten days or two weeks the general eruption, and this observation has been confirmed by other dermatologists.

The extent of the eruption varies very greatly. In some cases it is confined to one or two regions, but most frequently it is widely distributed. It occurs by preference on the front and sides of the abdomen, over the chest and on the buttocks, and on the sides of the neck. It may be universal, but it rarely develops on the face or below the elbows and knees. There is also considerable variation in different cases in the color of the lesions, which at times show an inflammatory red but more frequently a pinkish or fawn color. The eruption usually disappears in from two or three weeks to two or three months, but cases not infrequently last longer, even for four or six months.

The appearance of the eruption is usually preceded by a slight rise of temperature with general malaise, but these systemic manifestations are usually so slight as to pass almost unnoticed. There may be some enlargement of the lymphatic glands. This may be confined to the submaxillary and post-cervical glands. At times also the axillary and inguinal glands show slight painless enlargement. There is slight itching, particularly at night, or when the patient gets overheated, but it is not of severe character and causes little or no annoyance.

ETIOLOGY.—The etiology of the disease is unknown. Like the exanthemata and other toxic eruptions it occurs most frequently in children. It was thought by Hebra to be a mycotic affection, and this view still has its advocates. Its symmetrical distribution, the accompanying slight febrile disturbance, and the character of the eruption seem to indicate that it is closely allied to erythema multiforme.

HISTOPATHOLOGY.—Microscopically the changes found are those of a slight inflammatory process in the skin.

DIAGNOSIS.—The exceedingly trivial character of the systemic disturbances and the duration of the eruption serve to distinguish it from the exanthemata. From psoriasis and widely distributed forms of seborrhœic eczema occurring in small patches, it is distinguished by the lack of infiltration of the patches, the much lower grade of inflammation, and the character of the scales, the fine branny scales of pityriasis rosea presenting no similarity to the coarser scales of psoriasis and seborrhœic eczema. From tinea circinata it is distinguished by its much wider distribution, the rapid development of the lesions, and the absence of the ringworm fungus. It is most likely to be confused with the squamous and circinate syphilides, from which it is distinguished by more rapid development, less scaling, absence from the face and hands, and the absence of concomitant symptoms of secondary syphilis.

TREATMENT.—The disease requires very little treatment. Constitutional treatment should be symptomatic. Certain authorities think they have seen benefit from the use of salicylic-acid compounds. A mild antipruritic dusting powder, or lotion or salve is all that is necessary in the way of local treatment. William Allen Pusey.

PITYRIASIS RUBRA.—Pityriasis rubra is a dermatitis, usually subacute or chronic in intensity, in all but the most exceptional cases universal, and characterized by abundant dry desquamation. Other names by which the condition is known are dermatitis exfoliativa (Wilson), pityriasis rubra aigu (Devergie), erythrodermie exfoliante (Besnier). It is a rare disease.

SYMPTOMATOLOGY.—The disease may begin primarily

* R. Wehmer: Medicinal-Kalender, Berlin, 1901.

† Vierteljahrsschrift f. öff. Gesundheitspflege, 1902, vol. xxxiii., Suppl., p. 402.

as pityriasis rubra, or it may develop upon other inflammatory dermatoses. When occurring primarily it may begin in either of two ways. In some cases it begins as a diffuse hyperæmia, which increases until the skin becomes a bright red, and with the increase in redness there is the development of the characteristic desquamation. In other cases it begins as circumscribed red scaly patches. These spread peripherally and new patches form at the same time, until the entire surface becomes involved in the process. In the early stages of the disease the skin is of a bright, hyperæmic red color, which fades on pressure, and the induration is very slight. As the process becomes older the redness becomes of a deeper hue, and in some cases has presented a markedly venous character. There is also at times, even when arsenic has not been used, the development of marked pigmentation in the skin. The true color of the skin is more or less concealed by the abundant grayish scales which cover it. The abundance of this desquamation is one of the most salient characteristics of pityriasis rubra. The scales are dry and grayish in color; at times they are fine, but usually, except on the face, they occur as thin papery flakes. On the palms and soles the horny epidermis exfoliates in large flakes, which may at times amount to masks of the parts. The scales are easily detached and quickly reform. A quart or more of scales may be produced in twenty-four hours, so that they can be collected by the handful from the patient's bed. There is usually very slight induration of the skin, although after the disease has persisted for a long time the skin may become considerably indurated and stiffened as a result of the chronic inflammatory process. Rarely is there any free exudate. Except for perspiration the skin is dry, although a certain amount of weeping and even the formation of bullæ have been described. When we come, however, to cases of this character, accompanied by bullæ and free exudation, the border-line between this disease and pemphigus foliaceus becomes confusing.

There is more or less involvement of the appendages of the skin. The growth of the hair is interfered with and much falling of the hair takes place. At times the accumulation of scales underneath the nails causes them to be raised up and thrown off. Again the nails may become thin and softened and stunted or lost entirely. In some cases the nails become thick and rough and striated. The secretion of sweat is usually much diminished, but there may be an increase on such parts as the axillæ and genito-crural fold. The tongue in most cases is bright red, undoubtedly due to the exfoliation of the epithelium, which is washed away in the saliva.

The subjective symptoms are relatively unimportant. In rare cases the itching is severe, but usually it is of trivial character or absent. The sensation is more apt to be one of tenderness, burning, and stiffness of the skin. The onset of the disease is usually accompanied by a temporary febrile disturbance, which may recur with each exacerbation of the process. Except for such slight disturbances there may be no positive illness, although there is usually an indefinite lowering of the general physical tone, which becomes more marked as the disease progresses. Later on, the patients become anæmic, cachectic, and emaciated, and thus become the ready prey to intercurrent affections. Insanity, and other mental and nervous disturbances have been noted in a number of the cases.

The acute cases are often accompanied by very violent constitutional symptoms, with all the evidences of grave septic or nutritional disturbance. The temperature may range as high as 105° or 106° F. There may be great depression, diarrhœa, rigors, and a typhoid condition, and death may occur in one or two weeks.

ETIOLOGY.—The cause of the disease is unknown. It is probable that several conditions, essentially different, present this complex of symptoms. It is rare in children and occurs most frequently after middle life. It is more frequently observed in men than in women. Crocker thinks there is a close relationship between acute rheumatism and gout and pityriasis rubra, eleven out of eigh-

teen cases which he analyzed having shown this relationship. Jadassohn has pointed out the frequency of the association of tuberculosis in some form with pityriasis rubra. It is recognized that pityriasis rubra may supervene upon psoriasis, eczema, and other inflammatory affections. Brocq has seen a severe acute attack brought on by the vigorous application of chrysarobin, and Crocker has seen it follow vigorous inunctions with mercurial ointment and the external use of arsenic. Stelwagon has seen it develop on the extremities after the use of quinine by patients who had an idiosyncrasy as regards that drug. As an exciting cause, sudden chilling of the body has in some cases seemed to have a direct relationship to the development of the disease, and in other cases it has been excited by alcoholic debauches.

PATHOLOGY.—Microscopically the disease shows nothing to differentiate it from other simple inflammatory processes in the skin. There are the usual changes of a superficial dermatitis, and when the disease has persisted for a long time there are the connective-tissue changes characteristic of chronic inflammation of the skin. Several efforts have been made to discover central or peripheral nerve changes in connection with the disease, but without definite findings.

DIAGNOSIS.—The involvement of the entire skin, which occurs in all but the rarest cases, the profuse dry desquamation, the slight induration, together with the rapid development, are the prominent characteristics of the disease.

If it is admitted that psoriasis or a squamous eczema could become absolutely universal and of uniform type of eruption throughout, it is possible that they might be confused with pityriasis rubra. It is hardly likely, however, that this ever occurs. A universal psoriasis could be differentiated by the gradual development, the greater induration of the skin, and the thick, silvery white, closely adherent scales of that disease, and the hemorrhagic puncta following the forcible removal of the scales. It is hardly conceivable that an eczema could show a uniform type of eruption over the entire body, such as is seen in pityriasis rubra. Additional points of distinction from eczema would be the yellowish crusts of eczema, the presence of more or less free exudate, less rapid onset, greater induration of skin, more itching, and less evidence of constitutional disturbance.

The two conditions with which pityriasis rubra is likely to be confused are pemphigus foliaceus and pityriasis rubra pilaris. In pemphigus foliaceus there is the occurrence of flaccid bullæ, which, if not seen themselves, at least leave traces of their existence in undermined borders of epidermis and in the excretion of serum and pus, which dries in crusts upon the surface and gives rise to the sickening characteristic odor of pemphigus foliaceus. Pityriasis rubra pilaris does not develop so rapidly as pityriasis rubra, is not so likely to be universal, is accompanied by much greater induration of the skin, and shows the characteristic papules, which are entirely absent in pityriasis rubra. These rough, dry, horny papules, capping the hair follicles and giving the skin the nutmeg-grater appearance, that are seen on the back of the fingers and hands in pityriasis rubra pilaris, are entirely absent in pityriasis rubra.

TREATMENT.—The patients are made much more comfortable by emollient local applications. The essential thing is to keep the skin thoroughly lubricated. This may be done with vaseline, rose ointment, olive oil, lanolin, or mixtures of these in the form of liniments. The internal treatment is symptomatic, and is directed toward building up the patient's general health. Arsenic and quinine have both been advised empirically without very strong evidence of their having any specific effect. The patients should be carefully protected against chilling, and they do best when they stay in bed. There is little evidence that treatment has any effect except in relieving symptoms.

William Allen Pusey.

PITYRIASIS RUBRA PILARIS. See *Lichen Ruber Acuminatus*.

PONS AND MEDULLA, DISEASES OF THE.—It is a fortunate fact that the occurrence of vascular lesions, such as hemorrhage, embolus, and thrombosis, is rare in the neighborhood of the pons and medulla. They may of course occur in the presence of such a favoring element as cardio-vascular disease, which in turn may be due to a variety of causes, but when they are of any considerable size they are so quickly fatal that a determination of their exact location within the above structures is practically impossible. It is, moreover, not particularly easy, even though the lesion be so small as to be compatible with life, to locate it with absolute definiteness, and this in spite of the fact that the industry, both of the clinician and of the pathologist, has guided us to a remarkably clear comprehension of the physiologic values of the various nuclei, nerve fibres and tracts which lie in and traverse this anatomically complex territory.

In the case of extensive hemorrhage the victim is struck down so suddenly, and unconsciousness supervenes so rapidly that it is impossible to separate the damage to individual nuclei from the general havoc which the lesion entails. Certain features are, however, usually present which indicate in a measure the general situation of the extravasated blood. The respiration, for instance, rather quickly assumes the Cheyne-Stokes character, and this in itself should arouse a suspicion of the intimate relationship between the hemorrhage and the respiratory centre. Conjugate deviation of the eyes is also a fairly reliable indication of ponto-medullary hemorrhage, the eyes being turned toward the side opposite the lesion. The resultant paralysis is apt to be bilateral even though the hemorrhage be unilateral and differs from the flaccid type observed at the outset of an ordinary apoplexy in the tendency of the extremities to assume a degree of rigidity. This rigidity may be accompanied by a recurring shock-like tremor of a rather coarse type. The behavior of the reflexes is not sufficiently constant to be dependable, and there is nothing strikingly characteristic about the pulse and temperature.

In arterial lesions of lesser grades of severity the symptoms may be grouped in a variety of ways, dependent upon their site and extent. A lesion involving the pyramidal tract in the upper pons produces an ordinary hemiplegia, but if it be sufficiently extensive to include the facial nucleus, or even its roots, there usually results a so-called alternating hemiplegia; that is to say, a facial paralysis corresponding to the side of the lesion and a paralysis of the opposite side of the body.

A similar type is observed where the nucleus of the sixth nerve is included in the lesion. In other cases both the abducens and the facial nerves may be involved on the side of the vascular disturbance, and the resulting paralysis may be associated with hemiplegia of the opposite side of the body. Oftentimes the disturbance lies not exactly in the sixth nucleus, but near by in the conjoined centre for the sixth of the same side and the opposite rectus. This produces the conjugate deviation of the eyes away from the side of the lesion spoken of above.

The variety of clinical combinations which may occur in vascular lesions of the ponto-medullary region is relatively extensive. An examination of its anatomy reveals the fact that it contains the nuclei of the larger part of the cranial nerves, nuclei which serve also as trophic centres. It contains furthermore centres governing the respiration and the heart's action; likewise the great tracts and network of fibres which have to do with motion, sensation, and equilibration. The act of vomiting, the secretion of the saliva, and the vaso-motor activities of the body also doubtlessly depend upon centres located in this important region. Nowhere else in the central nervous system are so many important structures in such close proximity; hence it is easy to understand the eccentric grouping of symptoms arising from simultaneous destruction of nuclei and nerve tracts, both sensory and motor.

To attempt to give in detail all the clinical combina-

tions to which acute vascular lesions of this region may give rise would be as fruitless as it is impossible, the element of fortuitousness being too strongly in the ascendant. Generally speaking the onset of trouble is marked by rather severe vertigo, which may be accompanied by vomiting of equal severity. Consciousness is seldom profoundly disturbed, hence the patient is able to observe and give an account of his troubles. These may consist of the alternating hemiplegia above mentioned, or may be further complicated by a more or less extensive loss of sensation, by ataxia of the upper or lower extremities, by difficulty in speech and in swallowing, by diplopia, or by a complete loss of control of the facial muscles which externalize the emotions.

As stated above, it is impossible to construct a semiology which will fit every case. The point always to be emphasized is the eccentric grouping of symptoms indicating nuclear palsy combined with more or less extensive implications of the motor and sensory tracts.

The prognosis in this class of cases is fairly good as regards life. The damage to the nuclear elements is, however, practically permanent, the resultant paralysis being for the most part of the atrophic type.

Treatment is of little avail except in cases in which syphilis is the etiologic factor.

The medulla may be involved during the course of many diseases of the central nervous system, notably tabes, progressive muscular atrophy, multiple sclerosis, gliosis, and amyotrophic lateral sclerosis. It may also be the seat of tumor, abscess, or tuberculous disease. As none of these diseases can be classed as peculiar to the medulla no further consideration will be given them in this article.

The next disease of essentially medullary origin to be considered is the so-called

PROGRESSIVE BULBAR PARALYSIS.

(Labio-glosso-laryngeal [Pharyngeal] Paralysis.)

It is to be classed among the rare forms of nervous disease. Its victims are, in the large majority, found among the aged. A so-called infantile type will be spoken of later. As to its etiology nothing definite is known, hence the usual train of causative factors comes in for mention, namely, exposure to cold, traumatism, mental wear and tear; and even abuse of function of the lips, tongue and palate, although it appears that women are less commonly afflicted than men.

SYMPTOMATOLOGY.—The first thing that attracts the patient's attention is an unwonted fatigue after talking for any length of time, with a restricted ability to enunciate certain syllables. The initial disability lies, as a rule, in the articulation of the lingual consonants, *l*, *r*, *n*, and *t*. The tongue can at first still be protruded, but not to the normal extent, and there may be a difficulty in securing its proper apposition to the roof of the mouth for sounding the linguo-palatal consonants *t* and *d*. Up to this time the continuous sibilant *s* may be pronounced. With the increasing weakness of the lips whistling becomes impossible and there is an inability to utter the sounds in which the lips are chiefly concerned, such as *o*, *u*, *b*, *p*, and *m*. So imperfectly are the lips brought together and so sluggish is their separation that the labial explosives *b* and *p* degenerate into *m* and *u*. Finally weakness of the palate fails to shut off the nasal cavity, and a part of the expiratory air stream escaping through the nose gives a nasal quality to the voice, *b* and *p* sounding as *mb* and *mp*.

At this stage of the disease dysarthria is fully established. Words are run together and indistinctly articulated, with an intonation of a decidedly nasal quality. Single words may still by special effort be brought out clearly, but sustained speech of any clearness is impossible.

Either at this time or more commonly after the disease has been established a few months the patient experiences a difficulty in swallowing. Only by great effort can food be carried back through the pharynx to the

œsophageal opening. Fluids are constantly regurgitated through the nose, and at times are inhaled into the larynx causing choking and paroxysms of coughing. Ultimately neither fluid nor solid food can be successfully swallowed. Chewing also becomes progressively difficult.

Finally, both phonation and respiration become involved. The voice is weak and monotonous and lacks modulation. Hoarseness may develop and go on to complete aphonia. Toward the end respiration becomes labored, and not uncommonly severe attacks of strangulation occur.

Examination of the larynx shows in the beginning nothing abnormal; later, paresis of the adductors is obvious. The masticatory muscles betray their weakness by imperfect closure of the jaw and restricted lateral movements of the same.

Bulbar paralysis is of the degenerative type. Atrophy is, however, not an early symptom and almost never keeps pace with the paralysis. It is usually first observable in the tongue, which becomes lax and feels flabby and spongy; the fibrillary twitching is very striking. Ultimately the organ undergoes a marked grooving and furrowing, and its total volume is much diminished. The lip muscles are rarely affected until late in the course of the disease. They then become thin and toneless. The muscles of the jaw are only rarely markedly wasted, although a fibrillary twitching is not infrequently observed in them at an early stage.

The electrical excitability of the diseased muscles is never greatly altered. Late in the course of the disease there may be some quantitative change to faradism, but examination is never very satisfactory.

When the disease is far advanced the expression of the face is very characteristic and striking. The mouth is open, the lower lip sunken; and drooling is constant. The fixed and expressionless lower part of the face contrasts strangely with the still mobile muscles of the upper face and eyes, which alone afford mimic externalization of intellectual activity. The patient is very emotional and cries easily, but even then the mouth is but little discomposed, whereas the respiratory muscles are thrown into a sort of spasm to which is sometimes added a peculiar respiratory stridor. The shrunken, furrowed tongue lies motionless on the floor of the mouth, articulation is almost annihilated, and the feebly mumbled speech incomprehensible. The respiratory movement is hurried and the pulse may run as high as 140 per minute. Emaciation is very marked.

The above symptomatology develops on the basis of a paralysis of cranial nerves which are purely motor, and there is never implication of nerves which are sensory or sensorial. Curiously enough, however, in certain cases there is to be observed a peculiar heightening of tendon reflex irritability in the facial and masticatory muscles.

DIAGNOSIS.—Bulbar paralysis has so many features that are peculiar that its differentiation from other affections of the medulla should present no special difficulties. The gradual character of its onset and development, its practical restriction to persons of advanced age, the symmetrical implication of purely motor nerves with absence of sensory and sensorial disturbances, and the association of paralysis with atrophy are all factors which serve to crystallize out the disease from other affections of the same region. The features which further distinguish it from acute bulbar paralysis and from the pseudo-bulbar form will be considered later. Tumors of the medulla involve all structures in their neighborhood; hence, sensory nerves suffer as well as motor; furthermore tumors produce the usual train of symptoms characteristic of a general increase of intracranial pressure.

PATHOLOGICAL ANATOMY.—The essential morbid change in bulbar paralysis is a progressive decay of the motor nuclei of the facial, hypoglossal, and glosso-pharyngeal-vago-accessory, and occasionally of the trigeminal. The ganglion cells of these nuclei lose their processes, shrivel, and gradually disappear. The intranuclear reticulations and the intra- and extrabulbar roots undergo the same destruction, the change in the latter being suffi-

ciently marked in certain cases to be obvious macroscopically. In some cases the pyramidal tracts are involved.

PROGNOSIS.—The disease is, for the most part, steadily progressive and invariably ends fatally. Its duration varies from one to three years. Remissions rarely occur, although in any case there may be protracted periods during which there appears to be no advance in the symptoms. In quickly progressing cases the disease may run its course in less than a year. Death usually ensues by reason of asphyxia, bronchitis, inhalation pneumonia, inanition, or some intercurrent disease.

TREATMENT.—Many drugs have been tried, but none is of any special value. Strychnine in gradually increasing doses, arsenic, nitrate of silver, and the iodides are among those most strongly recommended. Forced feeding should be instituted early in the attempt to keep up the nutrition, and later, when dysphagia is established, the food should be introduced artificially into the stomach in order to avoid the very imminent danger of inhalation pneumonia.

A galvanic current of two or three milliamperes passed from one mastoid to the other is recommended by Oppenheim.

Vocal gymnastics may be tried in the effort to improve the speech.

The Hereditary (Familial) Type of Progressive Bulbar Paralysis.—A few cases of a peculiar hereditary form of progressive bulbar paralysis have been observed among members of the same family, usually among the offspring of consanguineous marriages. The victims are practically always true degenerates. The peculiarity of the disease in these cases is that it usually affects the upper facial territory first and its effects are most marked in this region, ophthalmoplegia, especially ptosis, being associated with the bulbar phenomena. These latter do not differ from those observed in the ordinary form.

The paralysis is in most cases of the atrophic type and is associated with partial reaction of degeneration.

In 1895 Oppenheim described an infantile form of pseudo-bulbar paralysis. It was observed by him in connection with cerebral infantile diplegia, and consisted of a bilateral paralysis or paresis of the muscles of the tongue, palate, pharynx, and larynx, which gave rise to the characteristic dysarthria, dysphagia, etc. The paralysis was associated with spastic athetotic movements of the affected muscles. Atrophy and fibrillary twitching were absent.

Oppenheim considers the pathologic basis of the disorder to be a bilateral disease or a developmental defect in the central convolutions.

THE ACUTE (APOPLECTIFORM) TYPE OF BULBAR PARALYSIS.—*Symptomatology.*—Certain cases have definite prodromes, such as pressure in the head, ringing in the ears, vertigo, sleeplessness, and spots before the eyes. The main symptoms develop suddenly. Intense vertigo or even a genuine apoplectic shock with complete loss of consciousness may usher in the attack. Vomiting may accompany the vertigo. In a few cases general convulsions of an epileptiform character have been observed.

Almost immediately after onset a labio-glosso-laryngeal paralysis is found in full development. This is manifested by characteristic dysarthria, dysphagia, etc. Although the paralysis is bilateral it rarely affects the two sides equally. In the majority of the cases the extremities are also involved in the same varying degrees. There may be paralysis of both arms with simple weakness of the legs, or there may be simple hemiplegia, the latter usually on the side opposite to that on which the bulbar nerves are most involved. The onset of all these symptoms may be less sudden, a few days or even a week being required for their full development.

Dyspnoea and even Cheyne-Stokes respiration, with marked increase of the pulse-rate, may be present early and may last for a very long time.

Various sensory disturbances are not unusual, and the patient may complain of painful paræsthesiæ in some parts of the body or extremities.

The expression of the face is characteristic; more so in

fact than in the early stage of the chronic type of bulbar paralysis, because the disease renders the facial muscles fixed and expressionless in a very short time.

The paralysis of lips, tongue, and soft palate is naturally not often associated with atrophy—first, because this phenomenon requires time; and, second, because it is the supranuclear part of the nerves which is usually affected. The nucleus itself may be directly affected, though rarely, and in such cases the characteristic atrophy with electrical changes may be found in the affected muscles.

The symptomatology is much more variable than in the chronic bulbar form, and naturally varies with the extent and seat of the lesion. The same eccentric grouping of bulbar nerve paralysis, with paralysis or paresis and sensory disturbance in the trunk and extremities spoken of under vascular lesions of the bulb in general, is to be expected.

Pathological Anatomy.—By far the commonest cause of the acute form of bulbar paralysis is thrombosis with softening. Both hemorrhage and embolism do occur, but with nothing like the same frequency. Policephalitis inferior acuta may determine the symptoms above described, and like symptoms are also ascribed to the pressure of a dilated atheromatous basilar artery.

Certain authors have observed the occurrence of an acute bulbar paralysis associated with weakness of the extremities during the course of typhoid; sometimes with a fatal outcome. In the latter cases streptococci and other organisms were found in various parts of the central nervous system without any very marked histological changes.

Prognosis.—Death may result, in very acute cases, within a short time from inhalation pneumonia or cardio-respiratory paralysis. In less severe cases the symptoms are slowly regressive and may gradually disappear, although restoration of function is seldom absolute in all the affected parts.

Treatment.—In cases suspected to be of syphilitic origin the prompt and free use of specific medication is demanded. Otherwise treatment should in the main follow the lines indicated in the therapy of cerebral vascular lesions in general. In the cases which arise in the course of an encephalitis of the ponto-medullary region antiphlogistic and derivative measures are appropriate. Very large doses of calomel may serve a useful purpose even in cases not syphilitic.

It is very important to make every effort to keep up the nutrition from the beginning. As paralysis of the muscles of deglutition may be absolute even from the outset, artificial feeding often becomes indispensable. In the later stages of surviving cases electricity may prove useful.

LABIO-GLOSSO-LARYNGEAL PARALYSIS OF PSEUDO-BULBAR AND CEREBRO-BULBAR ORIGIN.

In very rare cases after a patient has experienced a number of minor apoplectiform attacks a condition resembling the labio-glossolaryngeal paralysis of bulbar origin, without any implication of the bulb itself, may result.

The pathologic substratum of such cases is a diffuse atheromatosis of the cerebral vessels, which causes a gradual destruction of the cortical representations of the facial, hypoglossal, and motor trigeminal nerves.

To produce a fairly complete analogue of the genuine bulbar type both cortices must undergo considerable destruction in the regions above indicated, with secondary changes in the cortico-bulbar projections. As these changes are all distinctly supranuclear, atrophy and electrical changes in the affected muscles are wanting.

Clinically, while the above picture is in the developmental stage, the patient is observed to have a series of mild shocks which differ in nowise from the ordinary. It is only when the cumulative effects of these various shocks are manifest in a bilateral paralysis or paresis of the muscles of the face, tongue, and jaws with accom-

panying disturbance of speech, swallowing, etc., that the resemblance to the bulbar paralysis begins. Even then the likeness is not complete, since severe disturbance of the respiration and of phonation is ordinarily absent.

The mental state of such patients differs markedly from that observed in the genuine form of bulbar paralysis in that some type of psychosis, or even dementia, is usually present. So-called bulbar crying and laughing is, on the other hand, commonly present, and may be very marked.

The paralysis is not necessarily limited to the face and tongue areas, so that hemiplegia or diplegia may be present.

A further type—the cerebro-bulbar—described by Oppenheim, differs from the above only in the fact that with the cerebral arterial break-down is associated a similar condition in the bulb. The lesions are never large and the bulbar symptoms are of gradual onset.

Symptomatically, bulbar phenomena are found associated with marked mental deterioration. Both bodily and mentally the patient is in a most deplorable state. With the usual disturbance of speech, mastication, and deglutition is associated spastic paralysis of the extremities on one or both sides. Attacks of dyspnea and Cheyne-Stokes respiration either come on spontaneously or result from excitement, from paroxysms of spasmodic hiccough, or from attempts at motion. The optic nerves may undergo neuritis with consequent atrophy. The bladder and rectum may or may not be involved.

The prognosis in both the pseudo-bulbar and the cerebro-bulbar forms is very grave, although life may be prolonged for a considerable period of time.

The treatment recommended is that already described elsewhere.

ASTHENIC BULBAR PARALYSIS.

(Myasthenia Gravis Pseudoparalytica.)

To Erb (1879) is due the credit of calling attention to a symptom complex which so closely simulated that about to be described under asthenic bulbar paralysis that it must be considered its nosological analogue. It was not, however, until the appearance of Oppenheim's case in 1887 that this singular disease began to attract the attention which has been increasingly accorded to it up to the present moment.

Etiologically, little or nothing definite is known about it beyond the fact that it appears to result from the action of some toxic agent upon a congenitally predisposed nervous organism. Its association with tumors of the mediastinum and of the thymus gland has been noteworthy in specific instances. The predominance of the disease in early life is striking, but persons of advanced years are by no means exempt.

PATHOLOGY.—Up to the present time the most searching anatomic investigations have failed to reveal any organic changes in the medulla, bulbar nerves, or muscles. Congenital nervous defects and peculiarities have been observed in connection with certain cases, and a certain amount of stress has been laid upon the same as regards their morbid value, but it remains extremely doubtful if such stress has been rightly placed. The disease, in last analysis, appears to be a true neurosis.

SYMPTOMATOLOGY.—This comprises the usual dysarthria, dysphagia, and masticatory weakness with their associated palsy of the lips, tongue, palate and jaw observed in the ordinary types of bulbar paralysis. Added to this is a paralysis of the upper part of the face with imperfect closure of the eyelids. The paralysis also extends to the trunk and extremities, and attacks of dyspnea are frequent. In a certain number of cases the involvement of the eye muscles, notably ptosis, is the earliest and most striking symptom. Atrophy and reaction of degeneration in the affected nerves and muscles are absent throughout the entire course of the disease regardless of its duration.

Jolly in investigating the behavior of the affected

nerves and muscles to electrical stimulation observed a peculiarity which he designated "myasthenic reaction." He found that where a tetanizing faradic current was applied (either to nerves or muscles) at intervals of a few seconds, the muscular contraction grew progressively weaker and gradually vanished completely, but that the muscle regained its irritability after a short rest. He further found that if the current were passed through a muscle without interruption for the space of a minute or even less, the muscular contraction gradually died away, but was again obtainable by the same sort of stimulation after a minute's rest.

Analogous phenomena have been observed in voluntary attempts to use the muscles of the jaw or extremities. A patient may take one bite of an article of food and then be totally unable to bring the jaws together with any force, but after resting a while may regain enough strength to chew for a few moments.

The course of the disease is very peculiar. The complete development of symptoms may require many months, although in certain cases the time required has been much briefer. Remissions are common, and the full development of symptoms may be followed by a regression, but so treacherous is the malady that when recovery seems fully established, there may be a fresh outbreak of the most rapid character and the symptom complex again be complete in a startlingly short time. Intercurrent attacks of dyspnoea and tachycardia and febrile movements are common.

The disease has on the whole so many peculiarities that differentiation is not difficult. The combination of bulbar symptoms with weakness of the muscles of the trunk and extremities, the frequent involvement of the external ocular muscles (manifested mainly by ptosis), the retention by the affected muscles of their normal volume, the absence of reaction of degeneration in the presence of the peculiar "myasthenic reaction" mentioned above, the characteristic tiring of affected muscles on voluntary motion, the lack of definite sensory and sensorial disturbance, the absence of mental weakness and disease, and the complete lack of any tangible pathologic substratum in the brain, nerves, or muscles unite to form a clinical and anatomical picture that is *sui generis*.

The PROGNOSIS is always serious. Nevertheless the most alarming cases may end in complete recovery. Recovery is, however, never assured until there has been a freedom from symptoms for a period of many months. to the present time the majority of cases have terminated fatally.

TREATMENT.—The proper care of this type of bulbar paralysis requires unusual skill. A complete rest treatment, such as is followed in the severest form of neurasthenia, should be carried out in bad cases to the minutest detail. The patient should be allowed to do almost nothing for himself, even to swallowing food, which, by the way, should be selected so as to combine the maximum of nourishment with the least tax upon the digestive organs. Even the use of the stomach tube for artificial feeding is not devoid of danger, as its introduction may induce fatal suffocation. If mastication can be permitted with safety in a given case, care should be taken to allow the patient to rest between mouthfuls.

The drug treatment consists in the administration of tonics. In certain cases the preliminary production of diaphoresis has been beneficial. Against the use of electrical stimulation it cannot be too strongly cautioned.

Joseph W. Courtney.

PRESCRIPTION-WRITING.—A medical prescription is a written order to the pharmacist to take certain quantities of certain medicines, deal with them in certain pharmaceutical ways, "put up" the product in certain form for dispensing, and label the package with certain directions for use. Correctness in prescribing, therefore, relates to the three several matters of the *selection of the ingredients or composition* of the prescription, the *fixing of quantities or computation* of the prescription, and the

actual *writing of the order* in technical style, or *expression* of the prescription. These several topics will be considered *separatim*, in the order named.

I. THE COMPOSING OF A PRESCRIPTION.—Assuming that a prescription is intended, as always should be the case, to fulfil a single therapeutic purpose only, then the first point that presents is whether, under the circumstances of the case, a *single* medicine of the appropriate kind should be prescribed, or a *team* of such medicines. As regards this point, no general rule can be laid down—the matter will depend partly upon the nature of the therapeutic indication, and partly upon the respective peculiarities of the individual drug and the individual case. Thus to provoke *emesis*, a single drug is commonly prescribed; to excite *diuresis*, a team; while for *purging* the medicine will be single, if it be castor or croton oil, but multiple, if the selection be from among the resinous cathartics. The advantage of a team of similar medicines in prescription may be, on the one hand, a more *effective*, or, on the other, a more *kindly* accomplishment of the specific purpose in view, or it may be both possibilities combined. Thus, by a wise association in prescription of allied drugs, a maximum of therapeutic effect is attainable with a minimum of by-derangement. Having fixed upon the active member, or team of members, of the prescription, the next point is whether the medicinal working of the same may not be made even more effective or more kindly than would otherwise be the case, by the further addition to the prescription of some special substance. Such increase in both lines—effectiveness and kindness—may result by a chemical action upon the drug, on the one hand, or by a medicinal impression upon the system of the subject, on the other. Thus, as an instance of the working of a chemical action, stands the fact that the efficacy and kindness of operation of a dose of *salicylic acid* are both enhanced by the addition to the acid of a solution of a sodic carbonate, whereby the salicylic acid, which under its own form is both insoluble and irritant, becomes the more soluble, and at the same time far less harsh, body, sodium salicylate. As instances of an associated medicinal impression by an unrelated drug affecting the operation of the active member of a prescription may be cited the rather mysterious enhancement of the diuretic action of digitalis by the associate action of calomel, and the neutralizing of the griping of the rougher cathartics by the associated antispasmodic action of the pungent volatile oils, or of neurotics, such as belladonna or hyoscyamus. In the category of additions to a prescription for the purpose of enhancing *kindliness* of operation, belong *flavouring* substances. For an agreeable, or, at least, a not offensive potion, is not merely *pleasanter* than an ill-tasting one to swallow, but is also, by the very reason of non-offensiveness, far less likely than a nauseous dose to destroy appetite or derange digestion. The art of prescribing pleasant mixtures is therefore one of genuine advantage to the patient, as well as to the prescriber! Agreeability of taste is, of course, far more important in the case of fluid than of solid mixtures, and is attained, in the case of fluids, in part by wisdom in the selection of the active member of the prescription, and in part by the addition to the prescription of *sugar*, or of *syrup*, or of preparations of the more pleasantly flavored *aromatics*. Lastly, in composing a prescription, comes the thought of a possibly necessary substance to give *volume*, or, in the case of a powder or pill, to give *form*, or, in the case of a fluid mixture, to serve as a diluent, or as a solvent. The character and relative proportion of such a member of a prescription will vary so greatly in different cases, that no general rule affecting the selection of vehicles can be formulated. Members of a prescription for the several purposes named are commonly referred to as, respectively, the *basis*, the *adjuvant*, the *corrigent*, and the *excipient*, or *vehicle*, of the prescription. In the association of different substances in a prescription, no matter what the purpose of the several ingredients, regard must always be had for the mutual *chemical* relations of the things so brought into mutual contact, lest undesirable

reactions take place in the compounding (see *Incompatibility, Medicinal*).

II. THE COMPUTING OF AMOUNTS IN PRESCRIPTIONS.

—The first point in the matter of amounts in prescriptions is, in general, *not to order more of the medicine than present prognosis seems to call for*. Not unnaturally, the laity instinctively argue that the remedy should fit the case in *measure* as well as in *mode*, and hence, that an excess of medicine in the prescription is *prima-facie* evidence of a deficiency of skill on the part of the prescriber. They, furthermore, naturally object to the *paying* for the superfluous. Apart from these considerations, there are also many and obvious objections to a course that leaves half-used parcels of medicine to accumulate in a house, at the risk of inappropriate application on subsequent occasions, at ignorant hands. Hence, in cases in which an exact forecast of the amount of a medicine likely to be required is impossible, it is wiser to order no more than will surely be within bounds, letting the prescription be renewed if the amount prove too little. Assuming due regard to be paid to this principle, then the determination of amounts in a given prescription proceeds, by theory, thus: the amount of *basis* will be the product of the two factors, *quantity of dose* and *number of doses* required, and the several amounts of the other ingredients will be deduced from the amount of the basis, in accordance with the respective requirements of relative proportion. In putting this theory into practice, however, the important consideration has to be regarded, that quantities must be such as can conveniently be expressed in terms of the system of weight or of measure employed in the prescribing. This consideration determines, in general, the use of *round numbers*, and, in particular, of *such* round numbers as best conform to the relation between denominations in the particular system of weight or of measure followed in the prescription. For example, in general, no prescriber would fix a dose to be expressed by such a number as *one and one-tenth*, whether referring to grains or grams, nor would he ever estimate upon an aggregate of such an awkward number of doses as *seven*, or *eleven*, or *nineteen*, or *twenty-three*. And, for example again, in particular, the prescriber by the *apothecaries'* system of weight or of measure, recognizing the generally *duodecimal* ratio of the denominations of these scales, instinctively proportions the numbers of his prescription on a *duodecimal* basis. His ratios, that is, are as *one* to some one of the numbers 2, 4, 6, 8, 12, 18, 24, 60, 120, 180, 240, 480. On the other hand, if the *metric* system be the system followed, the *decimal* basis of this system almost of necessity entails the use of decimal ratios in proportioning amounts in prescription. Quantities are in this case fixed upon that are to each other as *one* to some number of this series of numbers: 2, 5, 10, 20, 25, 50, 75, 100, 200, 250, 500, 1,000. This fundamental difference in the figures to be used in working by the metric system as compared with the apothecaries' is a point very commonly overlooked by novices, in this country, in the art of prescribing by metric denominations. Because already fixed in the duodecimal habit through previous practice with the apothecaries' system, such novices are apt to compute in *duodecimal* ratios quantities which they then set down in terms of *decimally* related denominations—a proceeding wherein theoretical stupidity begets, as it should, practical disaster. For, by this proceeding, as it is hardly necessary to point out, there is wholly missed the one point of advantage which the metric system has to offer, namely, ease of computation by *decimal ratios*. A medicine, then, whose dose in prescription by apothecaries' weight is taken at *one grain*, is—or should be—in prescribing by metric weight, taken at *five centigrams*, and not at the *six* centigram amount by which the American metric prescriber, translating from terms of apothecaries' weight, so commonly figures. As well might an original metrician—to coin a convenient word—who essays a prescription by the apothecaries' system, first fix his dose, by his old metric habit, at five centigrams, and then, blindly insisting on exactly that quantum, despite its unsuitableness to the foreign system of weights, pre-

scribe in grains on the absurd basis of a *seven-eighths-grain* dose!

Such are the essential points of the theory of computing prescription amounts, and having due regard to these points, the prescription of *solid* mixtures for make-up into pills, powders, troches, suppositories, etc., is easy enough; but in the prescription of *fluid* mixtures many additional considerations enter into relation, as follows: In the first place, although it is not essential, yet it is elegant, and hence customary, to have a prescribed mixture aggregate *just a bottleful* of some one of the sizes of the medicine phials of the shops. Regard must therefore be had to the several sizes of such bottles. In the United States medicine phials are made of capacities conforming to *apothecaries' measure*, which capacities are severally as follows: *one, two, and four fluidrachms*, and *one, two, four, six, eight, and twelve fluidounces*. This fact of the conformity of medicine bottles to apothecaries' measure, makes, in this country, the prescribing of fluid mixtures readier by the apothecaries' than by the metric system. Phials for metric prescription should be of the natural metric capacities, severally, of *twenty-five, fifty, one hundred, two hundred, etc., cubic centimetres*.

The second special point affecting amounts in the case of fluid mixtures relates to the case of solids in solution, the point being the physical fact that, in dissolving a solid of a given measure in its condition of dry powder *does not augment the volume of the solvent by the full amount of such measure*, but, on the contrary, increases such volume so little that, in the ordinarily comparatively weak solutions used as medicines, the increment can safely be disregarded in the estimation of amounts for prescription.

The third point relates to the system by which, in a given case of a fluid mixture for internal giving, the *individual doses are to be measured*. This consideration does not obtain in the case of solids, since, in such case, doses are defined by a stated number of pills, powders, or troches—are, that is, already apportioned by the apothecary. But in the case of a fluid mixture, the medicine is necessarily dispensed in bulk (except when put up in capsules), and doses must be measured out by the administrator at the bedside. The point then presents itself of practical bearing, whether, in a given case, the dose is to be measured by a method of precision—by use of a graduated pipette, if the dose be quite small, or of a graduated vessel if of ordinary or large dimension—or whether the determination is to be by the conventional *drop* on the one hand or *spoonful* on the other. If a graduate is to be used, then the point now in question does not present itself; but if the *drop* or the *spoonful* is to measure the dose, then the consideration arises, in the apportioning of amounts in prescription, of the respective actual *dimensions* of these variable measures, under the conditions obtaining in the individual case. As regards the *drop*, it must be remembered that this measure varies in dimension, not only according to the viscosity and specific gravity of the fluid dropped, but also according to the *shape, extent, and character* of the surface from which the drop delivers itself, and even, furthermore, in the case of drops delivered from a phial, according to the *degree of fulness of the bottle* on the occasion of the dropping. A bottle with a flanged mouth, such as the ordinary medicine phial, yields, with the same fluid, a comparatively large drop when full or nearly so at the dropping, and a comparatively small one when at least half empty, the difference in the respective drop dimensions in the two instances being even as considerable as that between the numbers five and three. The reason for this difference in size of drops is that, from a full bottle, the contents begin to run out when the bottle is but slightly tipped, and accordingly, because of the position of the free edge of the lip, the nascent drop creeps into the re-entrant angle formed by the under surface of the lip and the side of the neck, and there has a chance to grow to a comparatively goodly size before gravity determines the fall. On the other hand, a phial half empty must be tipped to the horizontal before the

contents can run out, in which position the narrow rim of the lip points directly downward, and so presents but a small surface area for the fluid to cling to. Under these circumstances the fall will necessarily be in comparatively small drops. As regards the *spoonful*, it must be remembered that this measure, like the drop, is subject to variation, so that, in the case of prescriptions containing powerful medicines, amounts should be calculated on the basis of the *maximum capacity of the measure*. Whatever, then, may be the variation from the calculated dose in actual mensuration, will be on the safe side of a *shortage* instead of a possible *excess* of amount. Now a given spoon will naturally hold more of a *viscid* than of a *thin* fluid, and, in practical mensuration, will more readily hold its full complement when the fluid is poured *into* it, as from a bottle, than when the spoon is made to dip up the fluid from an open vessel. Hence, in the case of a *syrupy* mixture, with the dose to be taken *directly from the phial*, the conditions obtain where the spoonful will be at its maximum; while, on the other hand, in the instance of a thin watery dilution standing in a tumbler, with the dose to be dipped up by means of the spoon, the measure, although the same in name, may be very different indeed in fact. Another point, which should thoroughly be understood, relates to the size of the average spoon of to-day as compared with the spoon of the same denomination of two generations ago. Coming down from our ancestors is the estimate of the *tablespoonful* as the measure of half a fluidounce, or 16 c.c., and of the *teaspoonful* as that of a fluidrachm, or 4 c.c. These alleged equivalences, true of the average of spoonfuls of former days, are still handed down as present truth from teacher to student, and so come to be almost universally applied in prescription calculations. If, however, the reader will take from any chance pantry a sample of the average commoner kind of teaspoon, such as is generally relegated for service in the nursery, and will provide for himself an accurate graduate and a phial of water, he can learn for himself, in two minutes, the fact that the *teaspoonful* will run much nearer *six* to the fluidounce than the traditional *eight*—will equal the quantity of *five* rather than of *four* cubic centimetres. And, by the same token, the average *tablespoonful* of our own present spoons is of the dimensions of *three* rather than of *four* to the two-fluidounce measure—of *twenty* rather than of *sixteen* cubic centimetres. And indeed, in the case of thick fluids, such as strongly syrupy mixtures, or a fixed oil like castor oil, where also the fluid is poured into the spoon, the spoonful will considerably exceed even these larger estimates. In view of these facts, this writer, in his teaching, has always advised for prescription purposes the estimate of the equivalence of the *teaspoonful* as at 5 c.c., or at the rate of six to the fluidounce; and of the *tablespoonful* at 20 c.c., or at the rate of three to two fluidounces—six to four fluidounces.

By basing calculations on such assumed equivalences, any error in actual mensuration will be, as it should be, in the direction of a measure smaller rather than greater than intended. Furthermore, it is a happy fact that these equivalences give numerical relations far handier for purposes of calculation than the older estimates. In the case of the metric values, it goes without saying that for computation in decimal denominations, the numbers *five* and *twenty* are much more convenient for expressions of respective unit quantities than the numbers *four* and *sixteen*. And in the apothecaries' system the proportion of six to the fluidounce permits of a greater number of easily calculated combinations than the time-honored eight to the same measure, as is shown in the tables below.

A fourth consideration affecting the estimation of amounts in the prescription of fluid mixtures, obtains in the prescribing of a solid to be borne in solution in an inert fluid menstruum, the point being the matter of the proper proportion between solid and solvent. Of course, in the first place, the proportion must be compatible with the solubility, in the selected menstruum, of the given solid; and, also of course, in the second place, if the dose

is to be diluted extemporaneously for the taking, the concentration of the prescribed solution may be to any degree so compatible with solubility. If, however, as so often is the case, the prescription purposes a solution fit for direct administration without further dilution, then the consideration of *taste* enters into relation. An over-strong solution will be rough to the taste, and may also be irritant or even corrosive to the alimentary mucous membranes; while, on the other hand, if the solution be inordinately weak, the volume required for the carrying of a proper dose of the dissolved basis may be inconveniently large. Of course, in this matter the individual peculiarities of the constituents of a given prescription will require individual consideration;* but, in a general way, the truth obtains that the *teaspoonful* is best made the carrier of not more than—in convenient round numbers of the respective systems of weight—*twenty-five centigrams*, or *five grains*; and, similarly, the *tablespoonful* of not more than, respectively, *one gram*, or *twenty grains*, of a solid in solution. In the case of fairly bland substances, whose solubilities will at the same time permit, twice these quantities may be permissible; but such proportion should not be exceeded.

From this presentation of points affecting the prescription of fluid mixtures, it appears that, in cases in which it is expected that the whole bottleful is to be used, the estimate of amounts must harmonize a trio of conditions as follows: (1) The total must be just a bottleful; (2) it must aggregate *about* the number of doses therapeutically indicated; and (3) at the same time the amount of the active basis, while being such as to yield the proper strength of solution, must also be such as to admit of ready expression in terms of the system of weight or measure employed in the writing. In the use of the metric system this triple harmonization presents no difficulties, for the simple reason that since *any* amount is equally easy of expression by this system, it is only necessary to harmonize the first two considerations, letting the amount of active basis required foot up to what it will. Thus, for instance, let it be supposed that an indication seems to call for a medication three times a day for a few days; then all it is necessary to remember is that, if the active basis be one of small dose such that a *teaspoonful* is the more convenient carrier, a *fifty cubic centimetre* aggregate will fulfil the conditions of an even bottleful ~~on~~ the one hand, and about the requisite number of doses upon the other (ten *teaspoonfuls*, reckoning the *teaspoonful* at 5 c.c.). Then the individual dose of basis may be taken unconditionally by the therapeutic indication—it may be fixed at one, two, three, four, five, six, seven, eight, nine, ten, or any odd number of centigrams, and the expression of the aggregate will be equally easy, such aggregate being simply ten times the quantity for the individual dose, respectively, as follows: 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00 gm., etc. Similarly, if the case be one where a *tablespoonful* will be the more convenient measure for the dose, then a *two hundred cubic centimetre* volume will again yield ten doses (about the number indicated) of the selected dimension, and once more the individual dose of basis may be what it please, and the aggregate will be equally easy of expression. When, however, the *apothecaries'* system is followed in the prescription, at once a complication arises, for the reason that in apothecaries' weight all amounts are *not* equally easy of expression—some, indeed, being so awkward to express as practically to be unavailable. Thus, for instance, although by this system, as already pointed out, ratios are naturally taken in duodecimals, yet such a natural duodecimal multiple as *seventy-two*, representing grains, is a monstrosity for expression. In computing, therefore, by apothecaries' weight and measure, the prescriber is bound by the clumsiness of the denomination ratios of the system, and so, for cases in which the total basis exceeds a drachm, finds available for the fulfilment of the tripartite conditioning set forth above, a certain set of combinations only. These combinations the young prescriber must learn by rote. They are easily enough figured out for one's self;

but for convenience of reference there are set forth, in tabular form below, the combinations convenient when the individual dose of basis is to be one or other of the several amounts, *five, ten, fifteen, or twenty grains*. If the individual dose of basis be less than a grain or two, then the total amount of basis required, being but a moderate number of grains, is easy enough of expression, and the difficulty now under consideration does not obtain.

TABLE OF CONVENIENT COMBINATIONS FOR THE PRESCRIPTION OF FLUID MIXTURES BY APOTHECARIES' MEASURE AND WEIGHT.

1. Dose to be borne in an average teaspoonful, reckoning six teaspoonfuls to the fluidounce.

Capacity of phial in fluid-ounces.	Number of teaspoonfuls contained.	AMOUNT OF BASIS TO BE PRESCRIBED IN ORDER TO YIELD TO THE TEASPOONFUL THE SEVERAL DOSES OF—			
		Five grains.	Ten grains.	Fifteen grains.	Twenty grains.
1/16	3	gr. xv.	3 ss.	3 i.
1/8	6	3 ss.	3 i.	3 iss.	3 ij.
1/4	12	3 i.	3 ij.	3 iij.	3 ss.
3/8	24	3 ij.	3 ss.	3 vi.	3 i.
1/2	36	3 iij.	3 i.	3 ix.	3 iss.
5/8	48	3 ss.	3 iss.	3 x.	3 iij.
1	72	3 vi.	3 iss.	3 iij.

2. Dose to be borne in an average tablespoonful, reckoning one and a half tablespoonfuls to the fluidounce.

Capacity of phial in fluid-ounces.	Number of tablespoonfuls contained.	AMOUNT OF BASIS TO BE PRESCRIBED IN ORDER TO YIELD TO THE TABLESPOONFUL THE SEVERAL DOSES OF—			
		Five grains.	Ten grains.	Fifteen grains.	Twenty grains.
2	3	gr. xv.	3 ss.	3 iij.
3	6	3 ss.	3 i.	3 iss.	3 ij.
4	12	3 iss.	3 iij.
1/2	18	3 i.	3 ij.	3 iij.	3 ss.
		3 iss.	3 iij.	3 vi.

3. Dose to be borne in a measured fluidrachm.

Capacity of phial in fluid-ounces.	Number of fluidrachms contained.	AMOUNT OF BASIS TO BE PRESCRIBED IN ORDER TO YIELD TO THE FLUIDRACHM THE SEVERAL DOSES OF—			
		Five grains.	Ten grains.	Fifteen grains.	Twenty grains.
1/16	4	3 i.	3 ij.	3 i.	3 v.
1/8	8	3 ij.	3 iij.	3 ij.	3 vi.
1/4	16	3 iij.	3 ss.	3 ss.	3 vii.
3/8	32	3 viij.	3 x.	3 i.	3 viii.
1/2	48	3 ss.	3 i.	3 iss.	3 iij.
5/8	64	3 xvi.	3 iij.	3 iij.	3 iv.
1	96	3 i.	3 ij.	3 iij.	3 iij.

4. Dose to be borne in a measured half-fluidounce.

Capacity of phial in fluid-ounces.	Number of half-fluidounces contained.	AMOUNT OF BASIS TO BE PRESCRIBED IN ORDER TO YIELD TO THE HALF-FLUIDOUNCE THE SEVERAL DOSES OF—			
		Five grains.	Ten grains.	Fifteen grains.	Twenty grains.
1	2	gr. x.	3 i.	3 ss.	3 ij.
3/4	3	3 i.	3 ij.	3 i.	3 v.
1/2	4	3 ij.	3 iij.	3 ij.	3 vi.
3/8	6	3 iij.	3 ss.	3 iij.	3 vii.
1/4	12	3 i.	3 iij.	3 iij.	3 viii.
3/8	16	3 iij.	3 viij.	3 ss.	3 ix.
1/2	24	3 ij.	3 ss.	3 vi.	3 x.

III. THE EXPRESSING OF A PRESCRIPTION.—A prescription is an order, *dated and signed*, to the pharmacist to take certain quantities of certain several substances; to perform upon them certain pharmaceutical operations; to label the package with certain directions concerning

use, and to address it with the name of the patient. Upon this order the author may also have occasion to set down certain injunctions, such as "not to be renewed," or, "not to be shown to the patient," etc. In *form*, prescriptions are commonly written after the following paradigm:

[Not renewable without authority.]

For Mr. A. B.

Take
Of substance A, quantity x.
Of substance B, quantity y.
Of substance C, quantity z [etc.]
Do so-and-so [with them].....
Label [the package].....

[Signed] C.D., M.D.

No. 1 Blank Street.

[Dated] November 22d, 1886.

Instead of a written signature, a very common and a very good plan, followed by many practitioners, is to have prescription blanks printed for their personal use, bearing the imprint of name, address, and office hours. In such case the imprint is commonly at the head of the paper. In *language*, a prescription is commonly written in part in Latin, and in part in the vernacular. In the United States the use of the Latin is commonly confined to such portion of the prescription as has to do with directions to the pharmacist for the compounding and "putting up" of the medicine; but in many other countries the *directions for use* are also written in Latin. This latter foreign custom has nothing to commend itself, but, on the contrary, is intrinsically objectionable on the score of opening an unnecessary doorway for the entry of mistakes. For such directions must, of necessity, finally appear in the vernacular in the label upon the package which is to serve for the patient's guidance; so that, to write them in the prescription in Latin is to entail their translation back into the vernacular at the hands of the pharmacist for the purpose of transcription, all at the risk of mistakes. Far better is the American custom, whereby the prescriber can—and always ought—set down, in the vernacular, in *full necessary detail*, the directions for administration, which directions are then simply to be copied, *exactly as written*, in the labelling of the package. Another, and quite universal, custom is to express by *abbreviation* or by *symbol*, in the pharmaceutical portion of the prescription, what might be called *staple words*. Thus, in the foregoing paradigm, *take* is expressed by the symbol "R," which, originally the astronomical sign "♃," of the planet Jupiter (symbolical of the prayer to the deity Jove which in ancient times headed prescriptions), now bears its present peculiar form in order to do duty also as the initial letter of the Latin word *recipe*, signifying *take thou*. Next, titles of denominations of weight or measure are expressed by the commonly employed symbols for such denominations, and numeral adjectives by the so-called *Roman numerals* in the use of the *apothecaries'* system of weight or measure; but by the ordinary *Arabic numerals* when the prescription is by *metric* weight or measure, as is practically a necessity for the expression of the related integral and decimal fractions by which metric quantities are signified. Next, the word *misce*, signifying *mix thou*—the most commonly occurring word expressing requirement of pharmaceutical manipulation, is expressed by its initial letter *M.*, and similarly, and lastly, the word *signa*, signifying *label thou*, by its initial letter *S.* Other commonly employed abbreviations are "aa" for *ana*, latinized Greek for the phrase of *each*; "no." for *numero*, signifying *the number of*; "q. s." for *quantum sufficit*, signifying *as much as may be necessary*, and "p. r. n." for *pro re natâ*, signifying *according to need*.

It thus appears that all of the prescription requiring full dress in Latin is comprised in the titles of substances prescribed, and in the directions for the compounding. And for the correct latinizing of such items a critical knowledge of the Latin language, though, of course, of great advantage, is yet not indispensable. For, so far as relates to the expression of *medicine-titles*, all that is necessary is to know how to set these titles in proper *case*;

and, as concerns the expression of *pharmaceutical directions*, it is to be remembered that, in the great majority of instances, the directions for compounding requiring specification in prescription writing, are simple and set, so that their Latin phrasing is easily compassed by the knowledge of a few arbitrary words and phrases. Indeed, for all but seldom occurring exceptional directions, the latinizing can be effected by the words and phrases in the following list, properly coupled with Latin words signifying forms of medicines, presumably already learned.

LIST OF ODD WORDS AND PHRASES OF COMMON OCCURRENCE IN THE EXPRESSION OF PHARMACEUTICAL DIRECTIONS, IN PRESCRIPTIONS.—1. *Verbs, in imperative mood*; "object" to be in the *accusative* case (analogue of the English *objective*):

<i>Addē</i> , add.	<i>Filtra</i> , filter.
<i>Cōla</i> , strain.	<i>Mācēra</i> , macerate.
<i>Divide</i> , divide.	<i>Misce</i> , mix.
<i>Extēnde</i> , spread.	<i>Solve</i> , dissolve.
<i>Fac</i> , make.	<i>Tēre</i> , rub.

2. *Verbs, in subjunctive mood*, taking a *subject* or a *predicate*, *nominative*:

<i>Bulliat</i> , let [it] boil.
<i>Fiat</i> , let [it] be made [into].
<i>Fiant</i> , let [them] be made [into].

3. *Verbal adjective* (participle), to agree with its noun in gender, number, and case:

Dividendus (masculine); *-a* (feminine); *-um* (neuter), to be divided.

4. *Prepositions*: noun following to be in the *accusative* case:

<i>Ad</i> , to; up to.	<i>In</i> , into.	<i>Supra</i> , upon.
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5. *Prepositions*: noun following to be in the *ablative* case:

<i>Cum</i> , with.	<i>Pro</i> , for.
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6. *Miscellaneous Words and Phrases*:

<i>Ana</i> , of each.	<i>Guttatim</i> , by drops.
<i>Bēne</i> , well.	<i>Non</i> , not.
<i>Bis</i> , twice.	<i>Semel</i> , once.
<i>Dein</i> or <i>dēinde</i> , thereupon.	<i>Simul</i> , together.
<i>Et</i> , and.	<i>Statim</i> , at once.
<i>Graddit</i> , gradually.	<i>Ter</i> , thrice.

In the instance of a pharmaceutical operation which cannot be expressed in Latin by the application of the foregoing vocabulary, the wise course, even for the Latin scholar, is to forego elegance and write the direction in the vernacular. Otherwise it might chance that the prescription overstep the pharmacist's capacity for translation, to the obvious defeat of the compounding.

As regards the rendering, in proper Latin case, of the titles of the ingredient substances of a prescription, the points are as follows: There are, in Latin, six cases in the declension of nouns and adjectives, but of these cases four only are concerned in the latinizing of medicine titles. These four are, respectively, as follows: The *nominative* case, corresponding to the English *nominative*, is the case in which titular words stand in simple statement—by which, in short, names are learned. Thus we recognize prepared chalk by the Latin title *Creta preparata*, wherein the two words of the title are in the *nominative* case. Next, the *genitive* case corresponds to the English *objective* case after the preposition *of*, and is the case in which titular words most commonly stand in prescription writing. For, in the first place, *compound* titles, even in simple statement, commonly afford an instance of the *genitive*, as in the case of the title *tincture of opium*. Here the phrase *of opium* is rendered in Latin by the word *opium* set in the *genitive* case. Then, in the second place, in prescribing, the order for the "taking" of a given ingredient is, in the enormous majority of instances, a direction for the taking of a specified *quantity* of the substance in question. A prescription for a phial of laudanum, that is, will read: "Take of tincture of opium one-half fluidounce." In such case

the titular word of the preparation itself—in this instance the word *tincture*—will have to stand in the *genitive*, since now it, also, follows the preposition *of*. With the exception, therefore, of a few conditions when titular words stand, in prescription expression, in the *accusative*, the rule is that all titular nouns and adjectives which, in simple statement of the title, stand in the *nominative*, require, in prescription orders, to be set in the *genitive*.

The third Latin case that concerns the prescriber is the *accusative*, the Latin analogue of the English *objective following a transitive verb*. Titular nouns and adjectives take the *accusative* under the two following circumstances: First, when the order is not the common one to take a certain specified measure or weight of the thing, but to take *the thing itself* in a conditioned entirety. A common instance of this circumstance is where yolk or white of egg is an ingredient of a prescription. Here by the condition of things it is easiest to measure quantity by the natural measure of the egg substance itself. Hence, in prescribing yolk the order is commonly to *take the yolk of one egg*, or of two, or of three eggs, as the case may be; in which case the title word *yolk*, standing as the direct object of the transitive verb *take*, requires to be put in the *accusative*. Another commonly occurring instance where the *accusative* must appear, is where the prescriber writes for a certain *number* of a ready-made medicinal *entity*, such as pills or troches, of standard composition, and hence of independent title. Thus, to prescribe the pharmacopœial compound cathartic pill, the simplest way is to order directly the desired *number* of the already made pills, which the pharmacist keeps in stock. Such prescription, therefore, reads: "Take compound cathartic pills to the number of" so many, and so the word for *pills*, with its dependent adjectives, appearing as the immediate object of the verb *take*, stands in the *accusative*. The second circumstance determining the setting in the *accusative* of titular nouns and adjectives occurs, in one form of writing, in cases in which the prescription orders that a given substance be taken *up to the attainment of a certain total bulk or weight*. This form of order most commonly obtains in the prescription of fluid mixtures, where it is often convenient to order in specified quantities the necessary amounts, respectively, of basis or adjuvant; but, as regards the inert *vehicle* simply to direct the compounder to "take" the vehicle substance until the whole mixture shall attain the measure of the desired bottleful. In such case the order for the vehicle may be phrased in either of two styles—in the one of which the titular words will appear as usual in the *genitive*, but, in the other, in the *accusative*. The phrase in the latter style is according to the model, *take so-and-so up to [the measure of] so much*. Here the title of the substance "taken" is the immediate object of the verb *take*, and therefore stands in the *accusative*; the phrase *up to the measure of* being expressed by the preposition *ad*. The other style of phrasing the order is after this model: *Take of so-and-so as much as may be necessary to attain the measure of so much*. Here the title of the medicine once more follows the preposition *of*, and hence appears in the *genitive*. In the rendering of the order in this style, the Latin phrase *quantum sufficiat ad* (commonly abbreviated to *q. s. ad*) is the translation of the English "as much as may be necessary to attain the measure of."

The fourth and last Latin case that concerns the prescriber is the *ablative*, a case corresponding to the English *objective after certain prepositions*. The prepositions governing the *ablative* that occur in prescription writing are *cum*, "with," and *pro*, "for." The former of these occurs in a few titles, as for instance, *Hydrargyrum cum Cretâ*, mercury with chalk; *Emplastrum Picis cum Cantharide*, pitch plaster with cantharides; and the latter in the much-used phrase *pro re natâ*, "according to need." But as regards the *ablative*, the special point obtains that the circumstances of prescription phrasing never require the rendering in the *ablative* of a title word which in the title appears in a different case. The few instances of

the ablative in medicine titles are therefore fixed, and the ablatives so occurring are easily learned by rote.

The expression of case is, in Latin, effected by modification of the ending of the word itself which is to be declined, and in such modification, *adjectives* share as well as nouns. Different modifications are employed to signify case in the singular and plural number, respectively, and of such modifications there are, in ordinary, five distinct systems, constituting the five several *declensions* of nouns and adjectives, besides cases of irregular declension presented by certain pronouns and cardinal numerals. Of the five systematic declensions, one, the *fifth*, affords but a single example in prescription Latin, namely, the ablative *re* of the noun *res* in the oft-quoted phrase *pro re natâ*. Of the other four declensions, examples occur in prescription-writing of the *nominative*, *genitive*, *accusative*, and *ablative* cases, respectively, in the singular number, and of the *nominative*, *genitive*, and *accusative* in the plural. The following table shows the endings for the several cases so enumerated, so far as concerns nouns and adjectives embraced in the prescriber's vocabulary. Endings for nouns not in such vocabulary are purposely omitted, as are also the irregular declensions of pronouns. In the table the italicized letters *m.*, *f.*, and *n.*, signify respectively, that the case endings in the columns beneath are those of nouns or adjectives of the *masculine*, *feminine*, or *neuter* gender; for, as appears in the table, case endings often differ, even in the same declension, according to the gender of the word. The endings of the first and second declensions, severally, which appear *in parenthesis*, are the endings of certain Greek nouns, adopted into Latin with something of the Greek form retained. The table also gives a list of words of foreign origin applied as drug titles, which, following the Latin idiom in such case, make no change of ending to signify case—are, in short, *indeclinable*.

TABLE OF PARTS OF LATIN DECLENSIONS SO FAR AS EXEMPLIFIED BY WORDS USED IN PRESCRIPTION-WRITING.

1. Regular Declensions of Nouns and Adjectives.

	First declension.	Second declension.		Third declension.		Fourth declension.
	<i>f.</i>	<i>m.*</i>	<i>n.</i>	<i>m. and f.</i>	<i>n.</i>	<i>m.†</i>
SINGULAR.						
Nominative	-a (-e)	-us (-os)	-um (-on)	(various)	(various)	-us
Genitive	-æ (-es)	-i		-is		-ûs
Accusative	-am (-en)	-um (-on)		-em (like nom.)		-um
Ablative	-â	-o		-e		
PLURAL.						
Nominative	-æ	-i	-a	-es	-a	-us
Genitive	-arum	-orum		-um, -ium		-uum
Accusative	-as	-os	-a	-es	-a	-us

(Fifth Declension exemplified only in ablative singular *re* in phrase *pro re natâ*.)

*Except *juniperus*, *prunus*, *rhamnus*, *sambucus*, and *ulmus*, feminine.

†Except *quercus*, feminine.

2. Declension of Cardinal Numerals.

	Unus, One.			Duo, Two.			Tres, Three.	
	<i>m.</i>	<i>f.</i>	<i>n.</i>	<i>m.</i>	<i>f.</i>	<i>n.</i>	<i>m. and f.</i>	<i>n.</i>
Nominative	un-us	-a	-um	du-o	-æ	-o	tr-es	-ia
Genitive	-us			-orum	-arum	-orum	-ium	
Accusative	-um	-am	-um	-os	-as	-o	-es	-ia

All other cardinal numerals are indeclinable.

INDECLINABLE DRUG-TITLES—all neuter.

Alcohol,	Catechu,	Eucalyptol,
Amyl,	Chloral,	Kamala,
Buchu,	Cusso,	Kino,
Cajuputi,	Elixir,	Matico,

INDECLINABLE DRUG-TITLES—all neuter.—Continued.

Menthol,	Pyrogallol,	Sumbul,
Methyl,	Saiol,	Thymol.
Naphtol,	Sassafras,	

As appears at a glance from the foregoing table, in the case of any noun or adjective belonging to either of the three declensions numbered as *first*, *second*, and *fourth*, respectively, if the *nominative* be given, any other case can at once be formed by substituting the proper case ending for that of the *nominative*. In words of the *third* declension, however, this possibility in very many cases does not obtain. For in this declension the *nominative* often stands apart from the other cases in the way of having the very root, or "stem," of the word curtailed or modified in its construction. Thus, the stem *anthemid-*, giving genitive *anthemidis*, accusative *anthemidem*, and ablative *anthemide*, gives nominative *anthemis*—a word in which the full stem does not appear. Similarly, the root *flor-*, giving genitive *floris*, etc., gives nominative *flos*; and root *rho-*, giving genitive *rhois*, offers the much modified nominative form *rhus*. Hence, for the proper rendering in oblique case of nouns or adjectives of the *third* declension, it becomes necessary to learn arbitrarily the form of some one of the oblique cases—most conveniently the *genitive*—as well as that of the *nominative*.

A special point concerned in the expression of case obtains in the case of *adjectives*, to the effect that very many of these words form their case endings after different ones of the declension models, according to the *gender* of the noun to which the adjective is attached. In compound drug titles, therefore, which include an adjective, the gender of the noun modified by the adjective becomes necessary to know for the *intelligent*, proper rendering of the adjective's case ending. Of course, such knowledge is not essential, since the title, adjective, and all, can be learned by rote, and then, remembering the *nominative* form of the adjective, the necessary change to *genitive* or *accusative*, to suit the requirement of the prescription phrase, can be done by rule. But it saves a vast amount of unnecessary memorizing to understand the system, so far as system goes, by which genders of Latin nouns are determined. Reverting, then, to the above declension table, it appears that all prescription occurring nouns of the *first* declension are *feminine* in gender; all those of the *second* declension ending in *-um*, or *-on*, are *neuter*, and, with a few exceptions, all of the *second* declension ending in *-us*, or *-os*, and all of the *fourth* declension ending in *-us*, are *masculine*. The exceptions in the two latter instances are nouns in *-us*, representing ancient Latin *tree-names*, which, because of the ancient Latin conception of an inherent femininity in trees as things, take the feminine gender in spite of their etymologically masculine nominative ending. In the *third* declension all genders appear, and, although in nouns of certain nominative endings the ending carries with it the gender, yet in the case of many other nouns this is not so, and genders must be learned arbitrarily. Happily, however, the number of nouns of the third declension, among drug titles, which bear an associated adjective, are quite few.

From the above analysis it is evident that, in the case of a given *noun* in the *nominative*, the rendering of the same in an oblique case can proceed by rule according to the foregoing declension table, if only the declension of the noun be known; with the further item, in the instance of a noun of the *third* declension, that some one oblique case, as well as the *nominative*, be known, for the affording of the full stem of the word. Similarly, the proper case dress of any given *adjective* can be fixed if the scheme of declension of the adjective itself be known, on the one hand, and, on the other, the gender of the noun to which the adjective is to be affixed—adjectives requiring to agree with their respective nouns in gender, number, and case. This requisite information concerning nouns and adjectives of prescription use is afforded in the two following tables—the one giving a key to the declensions of nouns, with genders, and also, in the case of nouns of the third declension, genitive end-

ings—and the other showing the schemes of declension of adjectives.

TABLE SHOWING DECLENSION AND GENDER OF NOUNS OCCURRING IN TITLES OF U. S. PHARMACOPEIAL MEDICINES AND IN COMMON PRESCRIPTION TERMS.

Nominative singular ending in -a:

All First Declension and Feminine, except (of Greek origin) the following in -ma:

Physostig'ma (physostig'matis), 3d, n.	Catapla'sma (catapla'smatis), 3d, n.
Aspidosp'e'ma (aspidosp'e'rmat'is), 3d, n.	Gargari'sma (gargari'smatis), 3d, n.
E'nema (ene'matis), 3d, n.	Theobro'ma (theobro'matis), 3d, n.

Nominative Singular ending in -us:

All Second Declension, Masculine, except—

Juni'perus, 2d, f.	Rhus (rho'is), 3d, f. ("rhus gla-bra").
Pru'nus, "	Fru'ctus, 4th, m.
Rha'mnus, "	Spr'ritus, "
Sambu'cus, "	Que'reus, "
U'lmus, "	

Nominative Singular ending in -os:

Comprise only the following—

Flos (flo'ris), 3d, m.	Bos (bo'vis), 3d, m. or f.
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Nominative Singular ending in -um:

All Second Declension, Neuter.

Nominative Singular ending in -on:

Comprise only the following—

Eriodi'ctyon, 2d, n.	Eri'geron (erigero'ntis), 3d, n.
Hæmato'xylon, "	Li'mon (limo'nis), 3d, m.
Toxicode'ndron, "	

Nouns of all other endings are of Third Declension, and are as follows:

Ending in -e:

Lac (la'ctis), n.

Ending in -el:

Mel (me'llis), n.

Fei (fe'llis), n.

Ending in -en:

Se'men (se'minis), n.

Alu'men (alu'minis), n.

Ending in -o:

Confe'ctio (confectio'nis), f.	Mucila'go (mucila'ginis), f.
Lo'tio (lotio'nis), f.	Ca'rbo (carbo'nis), m.
Po'tio (potio'nis), f.	Pe'po (pepo'nis), m.
Tritura'tio (trituration'nis), f.	Sa'po (sapo'nis), m.

Ending in -r:

Æ'ther (æ'theris), m.	Li'quor (li'quoris), m.
Pi'per (pi'peris), n.	Su'lphur (su'lphuris), n.
Zi'ngiber (zingi'beris), n.	

Ending in -is:

Ace'tas (aceta'tis), m.	Pu'lvis (pu'lveris), m.
[and all salt-names in -as.]	Ca'nna'bis (ca'nna'bis), f.
(-as, genitive -adis)	Di'gita'lis (digita'lis), f.
Ascle'pias (asclepi'adis), f.	Hydra'stis (hydra'stis), f.
(-is, genitive -idis)	Sina'pis (sina'pis), f.
A'rse'nis (arseni'tis), m.	
[and all salt-names in -is.]	
(-is, genitive -idis)	
A'nthemis (anthe'midis), f.	
Ca'ntharis (cantha'ridis), f.	
Colocy'nthis (colocy'nthis), f.	
Hamame'lis (hamame'lidis), f.	
I'ris (i'ridis), f.	
Ma'cis (ma'cidis), f.	

Ending in -x:

Bo'rax (bora'cis), m.	Plx (pi'cis), f.
Sty'rax (styra'cis), m.	Ra'dix (radi'cis), f.
(-ex)	Nux (nu'cis), f.
Co'r'tex (co'r'ticis), m. and f.	Calx (ca'lcis), f.
Ru'mex (ru'micis), f.	

TABLE SHOWING SCHEMES OF DECLENSION AND GENDER OF ADJECTIVES OCCURRING IN U. S. PHARMACOPEIAL MEDICINAL TITLES AND IN PRESCRIPTION-PHRASES.

SCHEME I.—Second and First Declensions Combined.

Masculine.	Feminine.	Neuter.
-us [2d dec.]	-a [1st dec.]	-um (-on) [2d dec.]

SCHEME II.—Third Declension.

Masculine and Feminine.	Neuter.
-is (genitive -is).	-e (genitive -is).

SCHEME III.—Third Declension.

Masculine and Feminine.
-or (genitive -oris).

SCHEME IV.—Third Declension.

All Genders.

-ens (genitive singular -entis); (genitive plural -entium).

In commentary upon the declension schemes of adjectives set forth in the foregoing table, it may be stated that Scheme I. embraces by far the greater number of adjectives. In this scheme the neuter ending -on, borrowed from the Greek like the same ending among nouns of the second declension, finds among drug titles but a single example, *diachylon*. Scheme II. embraces a few adjectives only among those occurring in medicine titles, and affords an example of the nominative ending -e of the third declension, which does not occur among nouns of pharmacopeial titles. Scheme III. offers a single example only, viz., *fortior*. Of Scheme IV. pharmacopeial adjectives give but two examples, namely, *effervescens* and *recens*. A survey of the genders marked on the table shows that in every case a distinctive gender, where there is such, can be told from the adjective nominative ending.

A final point, concerning the expression of a prescription, is that, having regard to the fact that a slip of the pen on the part of the writer, or a slip of the understanding on the part of the pharmacist reader of a prescription, may convert what was meant as a missive of mercy into a death warrant, it behooves the prescriber most solemnly to execute his task *deliberately, thoughtfully, and, in chirography, legibly, abjuring all dangerous cloak-of-ignorance abbreviation of medicine-titles*; and, finally, to fail not of that trusty safeguard against error, a review of the paper after the writing. *Edward Curtis.*

PROTOZOA.—Standing distinctly as the lowest of all animal organisms, the protozoa constitute a branch differentiated from higher groups by the simplicity of organization in that the animal consists of but a single cell or a colony of simple cells. In the main the animals of this group are easily recognized, although some forms are so generalized, and partake of plant characteristics to such an extent as to render their classification doubtful; and, on the other hand, certain higher forms show the first stages in specialization among cells of the colony which ultimately leads to the differentiation of the metazoan organism.

The Protozoa are true cells and possess consequently neither organs nor tissues. In the discharge of all living functions by the single cell, however, one finds a physiologic complexity as striking as the morphologic simplicity. The latter is also less extreme in many cases where specialization has effected the production of individual features within the single cell, differentiations which subserve particular functions, and which are thus analogous to the organs of the metazoa. Such are denominated cell organs, or organelle, and are of great variety. Among these may be mentioned the locomotor structures, such as pseudopodia, flagella, and cilia, the numerous vacuoles of a nutritive and contractile type, the preformed, often highly modified openings for ingestion of food and egestion of solid waste matter, and various protective coverings of a permanent character or temporary and connected with reproduction.

As true cells all Protozoa possess one or more nuclei, and the earlier contention that there exists a special group of anuclear organisms, the monera of Haeckel, has not been confirmed by later study. The simple protozoon is with a single known exception (*Loxodes rostrum*) uninuclear, and the presence of many nuclei points to a colonial organism or to a reproductive phase, except that in one large group two forms of nuclei coexist and divide the functions otherwise resident in the single nucleus.

The reproduction of the Protozoa is again that of the

cell, viz., by division, which may be simple or multiple, and in varied form, either while free or in the encysted condition. Two types of division may alternate regularly or indefinitely in the life cycle of a given species, and in most subdivisions of the group certain so-called sexual processes have been demonstrated. These consist in general in the fusion of similar individuals (isogametes), or of dissimilar (macro- and microgametes), or merely in the mutual exchange of nuclear matter.

Knowledge of the completed life cycle gives an adequate conception of the species and its relationships, so that when but a single phase of the cycle is known any classification of the organism must be merely tentative. Evidence is accumulating to show that all Protozoa pass through two cycles denominated the sexual and the asexual cycle, which often differ radically in structure and appearance and always manifest strong contrasts in nuclear conditions. With the exception of the malarial organism, there is not a single parasitic protozoan of man in which the complete life cycle is known.

In regard to location parasitism among the Protozoa affords conditions not found otherwise. There are in this group not only organ parasites, as in the groups of helminthes, but also such forms as must be designated tissue parasites, cell parasites, and even nuclear parasites. Different phases in the life cycle of the same species may illustrate different modes of parasitism, as is the case with the malarial organisms, which at various epochs in the life history are successively cell parasites in the erythrocytes, organ parasites in the blood-vessels, and tissue parasites in the wall of the mosquito's midgut.

In general, however, the protozoan parasites repeat conditions already described for Metazoa. One finds the degeneration of organs superfluous under conditions of parasitic existence, the formation of organs of attachment, such as hooks, suckers, etc., the noteworthy fecundity already commented upon for metazoan parasites; and finally the alternation of generations and of hosts is a common feature among the Protozoa also.

An encysted condition of the entire individual or of a group of spores aids in the dispersal of the species, which are all inhabitants of a moist environment and cease activity at once on withdrawal of the water. This general habit renders it difficult to distinguish between mere commensals which find in the alimentary canal of higher forms conditions for their ordinary slime-inhabiting existence without exerting any influence upon the host, and such as are parasites in the true sense.

A true parasite draws its nourishment from the host and affects it at least to that extent. When this takes place, as with protozoan parasites largely, within a tissue or even a cell, morbid conditions are evoked, even though they remain local in some cases. That functional disturbances result is evinced by the relatively large number of protozoan diseases among animals and plants. These sometimes take the form of tissue proliferations, as has been clearly demonstrated for plants. An effort to trace similar effects in animals is found in the extensive literature on cancer parasites. Thus far, however, no sufficient evidence has been brought to establish the parasitic nature of such abnormal growths, and none of the supposed "parasites" can be clearly recognized as Protozoa. It should be noted in passing that in addition to the mechanical effect of cell parasites a chemical influence of at least equal importance is exercised by the excretions of the organism, the metabolic products set free in the protoplasm of the host cell. In some cases this is a factor of great importance, as also in the cases of bacterial diseases; its significance among Protozoa is not yet sufficiently investigated.

It is noteworthy that in many instances a protozoan infection is self-terminating, either that a type of immunity is acquired by the host, or that the reproductive cycle of the parasite reaches its limit without a change of host or alternation of generations. MacNeal and Novy have recently endeavored to determine experimentally the possibility of securing attenuated cultures

of one protozoan parasite (*Trypanosoma*) with absolutely negative results; the last generation from a culture more than a year old was even more virulent than the organism at the start.

Regarding means of infection but little definite evidence is at hand. It is inferred that encysted forms furnish the ordinary means for transferring the species to a new host, and yet in many cases experiments along this line have been without results. In other cases it is now known that the transfer takes place through some biting insect, which in some cases, if not all, acts as the host for another phase in the life history of the parasite, and is capable of transmitting the disease only after a period sufficient to allow of the development within its body of the specified portion of the life cycle.

In those cases in which the life history has been worked out, means of preventing the infection of the human host constitute the evident limitation to the spread of the disease caused by the parasite. The inauguration of a simple but effective prophylaxis for malaria and yellow fever ranks rightly as among the most brilliant achievements of scientific medicine. In cases in which the life history of the parasite is unknown, the prophylaxis is necessarily vague and uncertain. It is wise to emphasize here the importance of co-operative effort on the part of trained observers, both in medicine and in zoology, to elucidate fully the problems which necessarily offer almost insuperable obstacles to the investigator approaching them from the single standpoint.

The classification of Protozoa is still in a very imperfect condition. Our knowledge of the many recorded forms is confessedly incomplete, especially as to the life history. So long as the sexual cycle is unknown it is hazardous to attempt a natural classification of any form. It is equally erroneous to group together all types which manifest a certain superficial similarity in sexual stages. Especially open to criticism are attempts at classification based solely on parasitic, or disease-producing forms. Such a proposal as that recently made by Sambon, who would include in a single class, the Hæmoprotozoa, all blood-inhabiting Protozoa, is a serious step backward. This plan disregards all free-living Protozoa and does violence to all the evidence obtained from their study. The Hæmoprotozoa do not constitute a natural group: the definition of the group by Sambon is purely physiological and the similarity in habit which these forms manifest is no better justification of their taxonomic association than occurrence in the alimentary canal justified the long since abandoned group of Helminthes. The various subdivisions of Sambon's Hæmoprotozoa are forms of diverse origin which independently have become adapted to a parasitic existence in the blood stream, and in taxonomic consideration they must be relegated to the different classes of Protozoa from which they have sprung. They furnish at once striking evidence of parallel evolution and of convergence due to similar environment.

All the varied modifications within the branch of Protozoa may be grouped into four well-defined classes which are now almost universally recognized. These may be briefly outlined together with their major subdivisions, following in the main the classifications of Bütschli, Calkins, and Doflein, and noting principally those groups which contain forms found in the human body. Calkins regards these classes as phyla and raises correspondingly the value of all the subordinate groups. Although the older view is followed in the text, this change has much to recommend it.

Class I. Sarcodina.—Naked or shelled Protozoa, characterized in the free adult condition by the formation of changeable processes of protoplasm as organs of locomotion. These pseudopodia may be lobose, digitate, reticulate, or finely radiate, and may be formed over the entire surface of the body, or only at definite points. Reproduction takes place by simple division and by spore formation.

Subclass 1. Rhizopoda. Naked or shelled Sarcodina, having lobose or reticulate pseudopodia. The young

may be flagellate as well as amœboid, and are produced by multiple division of the active cell or during encystment. Included among Amœbina are naked forms (Gymnamœbina) with both free and parasitic species, and also shelled forms (Thecamœbina) only free-living.

Subclass 2. Heliozoa. Naked or shelled Sarcodina, typically spherical, with little change of form by amœboid movements. Pseudopodia fine, filiform, radiating from all parts, provided with axial filament and rarely changeable, exclusively free-living forms.

Subclass 3. Radiolaria. Marine Sarcodina with pseudopodia like those of Heliozoa, but always provided with internal chitinous capsule which encloses the nuclei. Skeleton of acanthin or silica sometimes absent. A very large group of free-living forms.

Subclass 4. Mycetozoa. Terrestrial saprophytic or parasitic forms, also known as Myxomycetes or slime moulds, and included under the fungi by some botanists. The motile amœboid or flagellate swarm spores, the plasmodia or colonies formed by the fusion of numerous amœboid individuals, and the holozoic mode of nutrition are characteristically animal features. On the other hand, the production of spores in sporangia, often provided with stalks and other plant-like structures, is taken to prove the plant nature of these forms. All known parasitic forms in this group attack plants.

Class II. Mastigophora.—Protozoa of variable form, naked or with cell membrane; they move by flagella, which vary in number from one to eight on each cell.* Mouth, contractile vacuole, and definitely formed nucleus usually present. Small forms with tendency to formation of colonies.

Subclass 1. Flagellata. Small organisms with one or more flagella at anterior end, usually actively motile, but capable of encystment. Reproduction by longitudinal fission of free form or by multiple division in encysted stage. Rarely transverse fission occurs.

Subclass 2. Dinoflagellata. Naked or shelled forms with two flagella, one of which extends out from the body, while the other is wrapped around the animal. No parasitic forms.

Subclass 3. Cystoflagellata. Large marine forms with parenchymatous protoplasm and firm membrane; marine; no parasitic forms.

Class III. Sporozoa.—Exclusively parasitic forms, in the adult condition without flagella or cilia, contractile vacuole, and opening for ingestion of solid food. Reproduction always by spore formation, usually within a firm membrane. Alternation of generations only exceptionally wanting. The young forms regularly begin the life cycle as cell parasites; other stages may be the same, or tissue or organ parasites.

Subclass I. Telosporidia.—At the end of a vegetative period the entire cell divides into sporocysts.

Order 1. Gregarinida. Vegetative stage intracellular at first, full-grown organism extracellular; fertilization isogamous, fertilized forms permanently extracellular. A large group of forms parasitic in alimentary and body cavities of invertebrates.

Order 2. Coccidiomorpha. Vegetative stage permanently intracellular; fertilization anisogamous; sexual generation permanently or temporarily intracellular. Many of the most important protozoan parasites of man fall in the limits of this group.

Subclass 2. Neosporidia.—Sporocysts are produced continually and at the expense of only part of the cell. In general these forms are not well known.

Order 1. Cnidosporidia. The spores possess one or more polar capsules which contain a coiled thread like a nematocyst. The sub-orders are: (1) Myxosporidia, parasitic in water-inhabiting vertebrates; and (2) microsporidia in certain invertebrates also. Both are not important here.

Order 2. Sarcosporidia. Parasitic in muscle cells of terrestrial vertebrates, probably without polar capsule. Little known, but important.

Class IV. Infusoria.—Protozoa with motor organs in the form of cilia, whether simple or united into membranes, membranelle, or cirri; with macro- and micro-nucleus; reproduction by division and by budding, combined with an exchange of nuclear matter known as conjugation.

Subclass 1. Ciliata. Cilia persistent except when encysted. Cytostome usually present. Mostly free forms; some parasites of man and other animals.

Subclass 2. Suctoria. Cilia only on young swarming stage. Food taken in by special sucking tubes; no cytostome. No human parasites.

According to this classification the forms which have been reported from man may be arranged as given in the following list, in which, however, chiefly those species are included which are definitely accepted. Some few doubtful forms of special significance are listed here; and still others are referred to in the text under general headings.

Class Sarcodina.

Subclass Rhizopoda.

Order Amœbina.

Suborder Gymnamœbina.

Entameba coli.

Entameba histolytica.

Amœba Miurai.

Leydenia gemmipara.

Class Mastigophora.

Subclass Flagellata.

Order Protomonadina.

Cercomonas hominis.

Monas pyophila.

Leishmania Donovanii.

Leishmania tropica.

Trypanosoma gambiense.

Spiroschaudinnia recurrentis.

Spiroschaudinnia Duttoni.

Treponema pallidum.

Treponema pertenuis.

Cystomonas urinaria.

Order Polymastigina.

Trichomonas vaginalis.

Trichomonas intestinalis.

Lambia duodenalis.

Class Sporozoa.

Subclass Telosporidia.

Order Coccidiomorpha.

Suborder Coccidia.

Eimeria Stiedæ.

Eimeria hominis.

Eimeria bigemina.

Suborder Hæmosporidia.

Plasmodium malariae.

Plasmodium vivax.

Plasmodium falciparum.

Cylasterion scarlatinale.

Subclass Neosporidia.

Order Sarcosporidia.

Sarcocystis Lindemanni.

Order Microsporidia.

Cytoryctes variolæ.

Rhinosporidium Kinealyi.

Class Infusoria.

Subclass Ciliata.

Order Holotricha.

Chilodon dentatus.

Order Heterotricha.

Nyetotherus faba.

Balantidium coli.

Balantidium minutum.

The relation of the Protozoa to disease is only just beginning to be investigated. At every point the student is met by the gross insufficiency of present knowledge; a host of isolated observations is on record. Some are clearly wrong, while others are indicative of important discoveries, though the presence of certain organisms during specific diseases needs confirmation, and equally their relation to the inception and progress of

**Multicilia lacustris* Cienkowski has many flagella, distributed over the whole body.

the malady. New methods must be worked out for the culture no less than the study of these forms, and the same sort of rigorous analysis is demanded in demonstrating their relation to disease which has been given to bacteria. It seems altogether probable that they will play a prominent rôle in medical investigation in the near future, but in the present state of our knowledge any review of the group must necessarily be only a tentative one.

The class of Sarcodina, or sarcode animals, is typically represented by the common free-living amœba, which has its parallel in the white blood cells. The most characteristic structural feature is the ability to protrude a portion of the body substance in the form of a process or pseudopodium by which locomotion is achieved, and also the food particles are seized and engulfed. The subdivision of the class rests primarily upon the precise character of the pseudopodia.

Under the order Amœbina are included such forms as possess lobose pseudopodia, and the sub-order of Gymnamœbina embraces such of these as are without a shell. All the human parasites which fall within the Sarcodina are included in a few closely related genera of this sub-order. While the structure is simple, and in agreement with that of the simple free-living forms of the group, it is impossible to demonstrate that this is not the result of degeneration from more highly differentiated forms by virtue of the parasitic mode of existence. The parasitic species are most probably to be traced back to slime-inhabiting, free-living forms, a transition from which to the present parasitic existence seems most immediate and simple in physiological adjustment.

The ordinary method of reproduction is by simple division, recurring at frequent intervals and conserving the rapid multiplication of the species. This form has long been known, and is to be observed frequently in all truly independent organisms of this type. Recent investigations have disclosed another reproductive type: under definite circumstances, possibly only after fusion of individuals or some exchange of nuclear matter, the amœba forms a cyst within which the nucleus undergoes multiple division, and ultimately the protoplasm arranges itself about the new nuclei, so as to give rise to an equal number of small amœbæ. When these desert the cyst there is left behind a residual mass of protoplasm. At first distinguishable slightly in structure as well as size, the small amœbæ thus produced soon grow to the size and appearance of the adult. The occurrence of this stage in the life cycle has not yet been demonstrated for parasitic amœbæ, except very recently for *Entamœba coli* and *E. histolytica*; but if present it may well be related to the spread of the species as found in the change of hosts. The necessity for such a stage would explain the ineffectual attempts which have been made to inoculate new hosts by direct transference of the ordinary parasitic form.

In the genus *Amœba* the separation of species is exceedingly difficult on account of the insignificant features available for purposes of differentiation. There are those who lump the forms found in man with such as occur in other mammals under a single species, and there are also those who contend that each host shelters a distinct parasitic species, and bring as evidence the individuality of parasitism in other groups. But on the other hand it may be urged that the amœbæ are not highly differentiated as parasites, and mere difference in host animal has long since been abandoned as a distinguishing mark between parasites from higher classes. It is certain that no positive statement can be made until more complete information is obtained regarding the life cycle of the species. At present no one can affirm that a given species does not possess a free-living generation as well, or even that it is not a normal free-living form which under favorable circumstances has taken up the parasitic mode of life; in which case it should be regarded as a mere accidental parasite. Furthermore of only one human parasite included within this group can it be said positively that it is more than a harmless com-

mensal. Although facts have been adduced to show that others also play a pathogenic rôle, the question must still be regarded as at least an open one.

Among the amœboid bodies which one finds in nature and in cultures many are only developmental stages rather than independent organisms, and the same may well be true of some of the parasitic forms. On the

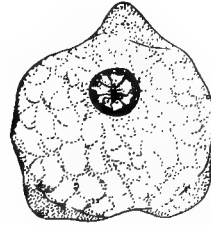


FIG. 5194.—“*Amœba coli*,” Stained Preparation. Magnified. (After Doflein.)*

other hand, the distinction between such organisms and various structural elements of the human body is often a very difficult task, and some of the purported parasitic species are in fact referable to the misinterpretation of the body cells referred to above.

In the new genus *Entamœba* are included two important human parasites, the life history of which has recently been well elucidated. The other imperfectly known species are left in the old collective genus *Amœba*, but fuller knowledge may result in the transfer of some or all to this same or other new genera according to the facts ascertained regarding the life history of the individual forms.

Entamœba coli (Lösch 1875).—(Syn.: *Amœba coli* Lösch 1875; [?] *Amœba dysenteriae* Councilman and Laflour 1891; *Entamœba hominis* Casagrandi e Barbagallo 1897; *Entamœba coli* Schaudinn 1903).

Form oval or pyriform (Fig. 5194); diameter from 0.0075 to 0.05 mm.; nucleus distinct in life, spherical, 0.002, usually 0.003–0.007 mm. in diameter, with heavy nuclear membrane and many small nucleoli. Ectosome not distinct save in pseudopodia, where it is conspicuous, everywhere less refractive than endoplasm. Pseu-



FIG. 5195.—“*Amœba coli*,” in Intestinal Mucus. Magnified. (From Braun after Lösch.)*

dopodia rare, usually one or two, broadly lobed and heavy (Fig. 5195). Endosome finely granular, with one or several non-contractile vacuoles, and many objects ingested as food; such as leucocytes, erythrocytes,

* In advance of the appearance of Schaudinn's figures it did not seem advisable to do more than quote the name given in the original from which these cuts were taken.

eosinophilia, bacteria, starch granules, faecal particles, epithelial cells, etc. (Fig. 5196). The digestion of erythrocytes is accomplished without excretion of any pigment masses.

Reproduction in the human intestine by simple division and by schizogony, with the formation normally of eight daughter cells. In fission the nucleus undergoes amitotic division, while in schizogony complicated nuclear changes are seen with the elimination of a portion of the chromatic substance. As a preliminary step to encystment all foreign bodies are extruded from the protoplasm, which thus becomes clear and transparent. These cysts, first discovered by Grassi, were carefully studied by Casagrandi and Barbagallo. They constitute the means of transmitting infection, as has been determined experimentally, first by Calandruccio who swallowed such encysted forms and found the developed amœbæ twelve days later in the faeces. The normal seat of this species is the upper region of the colon, and the vegetative forms appear in the faeces only when the latter are semi-fluid by reason of disease or of the administration of medicaments. The cysts which are so characteristic as to be confused with nothing in the faeces are capable of further development only when they contain eight nuclei. Other cysts have been determined experimentally by Schaudinn to be incapable of development, even though they actually constitute the major

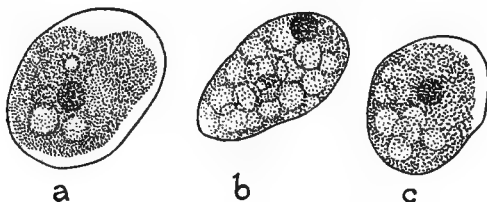


FIG. 5196.—“*Amœba coli*,” from Dysenteric Intestine, more or less filled with Erythrocytes; Nucleus also visible. Magnified. (From Doflein and Roemer).*

part (eighty per cent.) of those evacuated. In old dry faecal matter only the forms with eight nuclei are present, and in the colon of the next host eight small amœbæ are formed by division of the protoplasm and emerge to begin a new infection and a new vegetative period.

This species occurred in East Prussia in fifty per cent. of the cases examined; in Berlin the number found infected was 1 : 5, and on the Adriatic coast 2 : 3. The exact distribution of this species has not been further worked out, though the numerous reports lead one to believe that it is a cosmopolitan species.

Grassi was the first to identify the species from the normal human canal, and Schuberg confirmed this by a considerable series of cases. Casagrandi and Barbagallo demonstrated conclusively that it does not possess pathological characteristics, and quite recently Schaudinn in an exceedingly extensive and careful investigation showed the existence of two very similar species, hitherto generally confused, one of which, that under consideration, is a harmless commensal, and the other, to be considered next, a dangerous parasite. The first lives in the human host in health and is widely distributed; it multiplies excessively in various intestinal disturbances, and is brought to the exterior in faecal matter by any conditions which produce fluid or semi-fluid discharges from the canal. It can indeed coexist with the following species, which is pathological in the extreme. The present species was first carefully studied by Casagrandi and Barbagallo, and is easily recognized from their account. In the majority of cases reported, however, it is difficult to say which form was under examination, although it is probable that in many of them both species were studied and the description contains features characteristic of

both. This is the case with the full and valuable account given in Vol. I. of the HANDBOOK. (See *Amœba coli*.) To this admirable review of the subject have been added here only such features as aid in distinguishing the two recently differentiated species.

After extended study on abundant material in Manila Strong says he is not prepared to speak with certainty as to the entire non-pathogenic character of the so-called *Entamœba coli*, even though there are obvious reasons for supposing that *Entamœba histolytica* is the more harmful species for man. Musgrave and others go further in maintaining that all intestinal amœbæ are or may become pathogenic, and that the presence of amœbæ in stools is absolutely diagnostic of infection of the colon. The weight of evidence at present is against this view, and very recently Vedder in a discussion of the work done by Musgrave and Clegg considers in detail their arguments, maintaining positively the specific independence of the forms and pointing out what he regards as the fallacies in their conclusions. He emphasizes again the points of difference as given in the following table:

	<i>Entamœba coli</i> .	<i>Entamœba histolytica</i> .
Motility	By comparison in same stool the <i>E. histolytica</i> is more active.	By comparison in same stool the <i>E. coli</i> is more sluggish.
Endosarc and ectosarc.	Both endosarc and ectosarc are less coarse than in the <i>E. histolytica</i> .	Both endosarc and ectosarc are more granular and coarser than <i>E. coli</i> .
Blood cells within structure.	No blood cells have been noted within the structure of this species.	Red blood cells are found in this species, showing its partiality to these organic elements.
Nucleus	The picture is almost the complete opposite of that of <i>E. histolytica</i> .	The nucleus is always eccentric, the shape round, of small size, or not visible, the chromatin small in amount, and the nuclear membrane distinct.
The life cycle. . . .	Reproduction (a) by simple fission; (b) by encystment with the formation of eight small amœbæ. In the encysted form the parasites gain entrance to intestine protected against action of gastric juices; the adult forms are unable to infect.	Reproduction (a) by simple fission; (b) by sporulation, a process totally different from encystment, which, apparently, does not occur in <i>E. histolytica</i> . Schaudinn and Craig claim that these spores are capable of causing intestinal symptoms and lesions.
Pathogenicity	Found frequently in healthy individuals through long periods without symptoms.	The spores of this species have been shown by Schaudinn to cause intestinal lesions.

Until these facts, and especially the characteristic features of the life cycle, are shown to be incorrect the species established by Schaudinn must stand. These may be characterized as follows:

Entamœba histolytica Schaudinn 1903. (Syn.: [?]
Amœba dysenteriae Councilman and Lafleur 1891.)

In many general features like *E. coli*, often occurring together with the latter, and heretofore generally confused with it, yet distinguishable by the following features: Ectoplasm well developed and present as distinct plasma zone, more highly refractive than the endoplasm, viscous in consistence and glass-like in appearance. Nucleus rarely visible in life, almost homogeneous; little refractive, poor in chromatin, usually with a single nucleolus in centre, and with very delicate nuclear membrane, if indeed any is present. Reproduction by division and budding, the latter often multiple, and both following amitotic nuclear division. Cysts with eight daughter cells never found. Resting stages are formed when the faeces grow firmer; the progress of their forma-

*In advance of the appearance of Schaudinn's figures it did not seem advisable to do more than quote the name given in the original from which these cuts were taken.

tion begins by the rejection of chromatin from the nucleus until the entire plasma is filled with chromatin masses, and the nucleus itself degenerates and is absorbed or thrown out. The chromatin masses collect in the peripheral zone of the plasma and come to lie in ectoplasmic hillocks, which develop to free spherules on the surface of the cell. These structures measure only 0.003–0.007 mm. in diameter, and soon acquire a yellowish-brown membrane and a highly refractive semi-opaque appearance. The remainder of the amoeba goes to pieces. Schaudinn was able experimentally to evoke a severe dysentery by feeding these spores to cats, and maintains on good grounds that such spores constitute the only means of producing a new infection normally. Injections per anum of the vegetative form alone produced a typical case of the disease, as Jürgens showed first.

Craig has confirmed and amplified somewhat these morphological features which distinguish the two species, but Musgrave and Clegg (1906) question the correctness of many of these data and hold that the time has not yet arrived for a consistent differentiation of species among intestinal amoebæ.

While *E. coli* has no power to penetrate the healthy epithelium, *E. histolytica* is able to enter anywhere and force its way through. In this process the amoebæ push the cells apart, and even force them free from the layer. These features were first described correctly by Jürgens, who gave a full and accurate account of this species. His discoveries on the cat have been confirmed by the observations of Schaudinn on man also. The amoebæ were found in sound regions of the mucosa in the glands of Lieberkühn, and could be followed on into the submucosa. Undermining of the mucosa and abscess formation follow in later stages of the malady. These investigations demonstrate clearly that *E. histolytica* is a true tissue parasite, like the Myxosporidia, and indeed the most dangerous of all Protozoa yet known, and that it is the cause of ulcerous amoebic enteritis.

Jürgens is the only author who in the opinion of Schaudinn has characterized this species in recognizable form, although the species was probably before many authors, who were unable to differentiate it clearly from the other species, *E. coli*, with which it was certainly associated in some cases reported.

The material from which the pathological species was obtained by Schaudinn came from a limited number of cases of tropical dysentery acquired in Egypt, China, and Siam. The real geographical distribution of the species is thus evidently but imperfectly known.

An amoebic dysentery is endemic in India, Egypt, the Philippine Islands, Brazil, and even the southern United States, while sporadic cases and even occasional epidemics occur as far north as New England and East Prussia. That the disease is caused by *Entamoeba histolytica* is a mere conjecture in the absence of precise studies on the particular organism in each locality. In Manila the water supply constitutes the greatest source of infection, and Musgrave's experimental infection of monkeys with amoebæ from cultures made from the city water demonstrated that some of the amoebæ found in the water are pathogenic, and probably of this species from the character of the disease and its lesions.

It is difficult to pass satisfactorily upon the specific character of the forms hitherto observed in the United States, and only two references will be made. The observations of Craig (*Medical News*, March 16th, 1901) seem to have been made on *Entamoeba coli* of Schaudinn, in which the former described as "oval spots" the formation of the encysted daughter cells already well known from the work of Casagrandi and Barbagallo. The splendid monograph of Councilman and Lafleur in my opinion deals unmistakably with *E. histolytica* of Schaudinn. The description of the amoebæ is very detailed and precise, and apparently agrees minutely with the characters, such as the form, appearance, and position of the nucleus, advanced by Schaudinn to separate the pathogenic *E. histolytica* from the harmless *E. coli*. The absence of any reference by such careful observers to the

formation of cysts, which is easily observed in *E. coli*, must be regarded as confirmative evidence of the presence of the other species. If this opinion with regard to the identity of the forms proves to be correct, the specific name given by Councilman and Lafleur will have to be used in preference to the later name given by Schaudinn, and the species will be known as *E. dysenteriae* (Councilman and Lafleur 1891). Although illustrated by very inadequate figures, the pathological lesions caused by this species are described by these authors with great fullness and care, and anticipate very largely the work of Jürgens, to which Schaudinn accords such well-merited praise. On the other hand, Lafleur stated in a later paper that no clear morphological distinction had been discovered between amoebæ from stools of healthy and of dysenteric individuals. In personal discussion Schaudinn stated to the writer that after extended and most careful study of their description and figures he was unable to find the characteristic features which would indicate that Councilman and Lafleur had before them *Entamoeba histolytica*. If these statements are accepted, the specific name *dysenteriae* is inadmissible.

Entamoeba undulans Castellani 1905 was discovered in a case of chronic dysentery in Ceylon, in company with *Entamoeba histolytica* and *Trichomonas intestinalis*. It was oval or spheroidal, 25 to 30 μ in diameter, and emitted periodically a single narrow elongated pseudopodium which was soon retracted. No flagella were present, but an undulating membrane in constant rapid motion spanned obliquely the length of the body. Although larger than either of the other parasitic protozoans present, this may have been an involution form. In any event it does not fall within the genus *Entamoeba* as at present defined.

Paramoeba hominis Craig 1906 is a form reported from natives of the Philippine Islands. The amoeboid stage is 15 to 25 μ in diameter, with distinct ectoplasm, endoplasm, and nucleus; later it develops a refractive, hyaline, doubly contoured cyst wall within which many small spherules are formed. After they are liberated by rupture of the cyst, they move actively by means of a long delicate flagellum. The further life history is conjectural. Craig is not able to say whether this form is pathogenic or not.

The following forms included under the generic name *Amoeba* are classified thus rather tentatively, as our knowledge of the life history at least is too limited to allow of greater precision. Probably some at least are related to the species just described, if not identical with them.

Amoeba Miurai Ijima 1898.—Normally isolated individuals (Fig. 5197), adhering in conglomerate-like clusters only when dead or dying. Living specimens, spher-

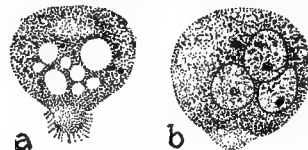


FIG. 5197.—" *Amoeba Miurai*. a, Living; b, from specimen preserved in acetic acid. $\times 500$. (After Ijima.)

ical or ellipsoidal, having at one pole a small rounded protuberance or villous knob, which is closely set with fine pseudopodia. Diameter 0.015–0.038 mm. Villous knob papilliform or hemispherical, 0.01 mm. in diameter at base, but capable of entire retraction at times, or the fine pseudopodia may be entirely withdrawn. Nucleus round, oval, or reniform, 0.008–0.015 mm. in diameter, two or three being found in the single cell as often as one. Ectoplasm visible only in villous knob; endoplasm finely granular with one to several conspicuous non-contractile vacuoles and minute oil-like corpuscles.

This form was found by Miura and described by Ijima. It occurred in the serous fluid accumulation of peritoneal and pleural cavities in a woman, twenty-six years

old, who died from peritonitis and pleuritis endotheliomatosa. The amœbæ were absent at first from the fæces, but made their appearance two days before the patient's death, concomitantly with hemorrhage in the intestine. Living and dead individuals were found together in the freshest serous fluid under rigid precautions against injurious influences, and this is regarded by Ijima as evidence of the abnormal occurrence of the parasite. It has not been reported since then, and is explained by some authors on the basis that the supposed amœbæ were only "exudate cells." Lühe states that this is unquestionably the case.

A considerable number of so-called amœbæ have been reported from various organs in man, and usually pathogenic characteristics have been attributed to them. They are known mostly from single records of their occurrence, and often lack both name and recognizable description. It has been suggested that they are commensals, and of secondary importance. It is equally probable that some at least are occasional or accidental parasites, and devoid of general importance in human pathology. Owing to the general uniformity of structure in this group all but the most careful descriptions are worthless for future study and comparison with other species. A few of the best accounts of these uncertain forms are noted here for reference.

Amœba Kartulisii Doflein 1901.—Diameter 0.03–0.038 mm. without distinct ectosarc and endosarc. Plasma coarsely granular, with very small nucleus (or nucleolus?), demonstrable only by staining. Movement more rapid than in *Entamœba coli*. Usually only one or a few pseudopodia, long, digitate, and rapid in formation. Reproduction not observed.

This species was found by Kartulis in Alexandria, where it occurred in an Arabian, in a tumor the size of an orange, on the right mandible. In the thick pus and on fragments of extracted bone the amœbæ occurred together with numerous bacteria. They had been feeding on blood and pus corpuscles. Although apparently distinct from *Entamœba coli*, Doflein inclines to regard their connection as not impossible, and views as even more probable this interpretation of the amœbæ from an abscess in the oral cavity reported by Flexner. These were described as larger than leucocytes, with granular vacuolated plasma and a nucleus demonstrable only with some uncertainty. Although in both these cases the presence of *Entamœba coli* in the host had not been shown by any antecedent dysentery or fæcal examination, it has already been stated that this species may be present in the normal intestine, and its occurrence outside the canal in abscesses is abundantly demonstrated by other cases. It is less probable this form may have been *Entamœba histolytica*, though the description is not distinctive, as the absence of lesions in the canal can hardly be explained if the pathogenic species was present.

Another record by Verdun and Bruyant (1907) of *Amœba coli* from malar abscesses in man strengthens the view that Kartulis's case also concerned *Entamœba coli*.

Amœba urogenitalis Baelz 1883.—Diameter 0.022–0.05 mm. Plasma coarsely granular, containing one or several nuclei, excretory products, and erythrocytes. Movement slow, by formation of short pseudopodia. Encysted forms possibly occur.

Originally found in numbers in the bloody urine and vaginal mucus of a Japanese woman, twenty-three years old, who shortly before her demise from tuberculosis manifested hamaturia with strong cystic tenesmus. (Cf. Vol. I., p. 233, HANDBOOK.) Similar cases have been reported by many authors. In Jürgens's case chronic cystitis was associated with small mucous cysts filled with amœbæ; these were also present in the entire vagina. The descriptions are scanty and do not render a differentiation between these forms and *Entamœba coli* and *E. histolytica*, either structurally or clinically easy at present. Pathogenic characteristics are certainly not distinctly shown, and in so far this case belongs more probably to *E. coli* if to either. Better knowledge of the species and more careful examination of the reports of

previous observers may make it possible to refer some such cases to a definite species; but many will always remain uncertain.

Amœba buccalis Sternberg 1862; *Amœba dentalis* Grassi 1879; *Amœba gingivalis* Grassi 1849.—All these species were discovered in tartar scraped from the surface of human teeth. They have not been reported a second time, and Celli and FioCCA state specifically that they have failed to find amœboid organisms in the oral cavity.



FIG. 5198.—*Leydenia gemmipara*; a, at rest; b, in movement. Magnified. From Doflein and Schaudinn.)

Grassi himself suggested the possibility of confusion with salivary corpuscles.

Amœba pulmonalis Artault 1898.—In an examination of the contents of a large pulmonary cavity a small number of amœbæ were found among the leucocytes, which were distinguishable by firm contour, much finer and more uniform granulation, and a distinct nucleus or vacuole. In appearance like the epithelial cells found in sputum, they manifested changes in form and position through the slow formation of pseudopodia. They were also more highly refractive, and resisted methylene blue or fuchsin longer than leucocytes, but when preserved they stained readily and were indistinguishable from the latter. Despite the conjectures of the discoverer their real nature remains entirely unknown.

Leydenia gemmipara Schaudinn 1896.—Irregularly spherical or polygonal in form when resting (Fig. 5198, a), surface with prominent verrucosities. Ectosarc and endosarc not distinctly limited, but pseudopodia more hyaline than the opaque body with numerous highly refractive yellowish granules. Diameter of body, 0.003–0.036 mm. Nucleus single, spherical, distinct in life, and in the preserved specimen regularly one-fifth the diameter of the body; movement very slow, produced by formation of a broad, hyaline lamella at the anterior margin; streams of granular endosarc extend to the margin of this lamella (Fig. 5198, b), and may even project beyond it as pointed pseudopodia. The endoplasm contains granules, crystalline bodies, interpreted as excretory, and numerous vacuoles which increase in size toward the centre. A pulsating vacuole is present and contracts at intervals of about fifteen minutes.

Two or more individuals frequently unite without fusion of the nuclei, and plasmodia are formed by the union of many single individuals. Both division and gemmation occur. In the former the size of the resulting amœbæ may be very different, but is always proportional to the size of the nuclei (5:1). The nucleus divides directly, and the bud which originates as a protuberance from the surface of the amœba gradually works free and becomes an independent individual, which may at once undergo multiple division, giving rise to a mass of small spore-like forms (Fig. 5199).

Many years ago Lieberkühn observed in ascites fluid associated with malignant tumors peculiar cells; and similar structures were seen later by others. In 1896 Leyden and Schaudinn, on the basis of an exact investigation of these bodies in a particular case, determined them as a new parasitic rhizopod. Leyden had found them in the ascitic fluid of two patients in whom positive evidence of gastric carcinoma and of tumors in the peritoneal cavity was furnished. The amœbæ appeared in numbers in fluid drawn off from the cavity, and could be kept alive in fluid preserved several days under aseptic

tic conditions. Schaudinn studied the amœbæ carefully and pronounced them to be unmistakably parasitic forms. Some later critics have inclined to reject this view, and regard them as descendants of the human tissue cells or pathological neoplasms. L. Pfeiffer especially has maintained that similar large amœboid cells ("exudate cells") occur in variola, vaccinia, varicella, herpes zoster, etc., and yet the contractile vacuole, peculiar nuclear structure, and reproductive processes of *Leydenia* indicate unmistakably an independent organism, as well as many other features in which it resembles various related free-living forms. Originally Leyden and Schaudinn were inclined to connect this form with

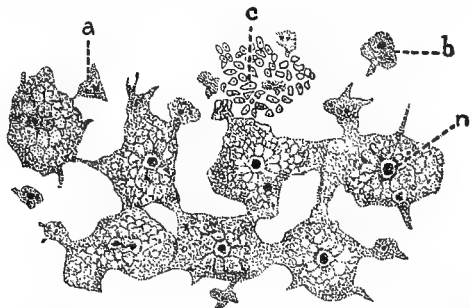


FIG. 5199.—*Leydenia gemmipara*. a, b, c. Young individuals formed by gemmulation. n, Nucleus. Magnified. (From Dofflein after Schaudinn.)

carcinoma, but expressed no positive opinion on this point. Unfortunately it has not been studied by subsequent investigators, and in fact has been found but twice since then, although often sought for under similar circumstances. Schaudinn later advanced the view that this form is probably an accidental commensal.

As an appendix to the Sarcodina may be included certain bodies described in 1903 by Negri as found in the nervous system of animals which had died of hydrophobia. They measure usually from 4 to 10 μ in diameter, but vary from the limits of visibility to 25 μ . They are generally round or oval, though at times irregular, and manifest a distinct internal structure. Annular forms and rosettes are frequently seen. These structures are generally designated Negri bodies. They occur singly or by two or three in the protoplasm of nerve cells, being most numerous and largest in the hippocampus major. Purkinje cells of the cerebellum, pyramidal cells of the cortex, and cells of the pons, cord, spinal and gasserian ganglia are also infected. They have been found in dogs, cats, rabbits, and man, both in natural and experimental rabies, and do not occur under any other known conditions. Nevertheless their apparent absence occasionally in cases of undoubted rabies is acknowledged even by Negri, who attributed the fact to anomalous distribution of the organisms. The bodies appear in the nerve cells from one to three days before the outbreak of the disease.

Efforts made to arrange the various forms in a cycle have met with scant approval, and it has been shown that the virus passes through a Berkefeld filter No. 5, indicating an ultra-microscopic size for one stage at least. Some view these structures as degeneration products, but the original views of Negri that they are Protozoa, and also true etiological factors of rabies, are gaining ground with further study. They are clearly specific for this disease, and as such of great diagnostic importance. The time is not ripe for assigning them a very definite place. However, A. W. Williams has recently reported the occurrence in the Negri bodies of definite chromatoid granules or chromidia. The type and history of these structures seem to indicate according to Calkins that the Negri bodies should be classified as Rhizopoda.

This form, which has received the name of *Neuroryctes hydrophobiae* Williams 1906, furnishes important evidence

on the character and relationship of the smallpox parasite, *Cytoryctes variolæ*. In his most recent publication, Calkins interprets the latter also as a rhizopod in which only the asexual or negative phase of the life history is known. This is characterized by the development of the chromidium and the formation of small reproductive spores (gemmules) which repeat the cytoplasmic cycle. The intranuclear forms belong probably to the sexual cycle and may be a different cycle of the organism occurring in variola and not in vaccinia. The vesicular forms may be either poorly fixed organisms or degeneration forms.

In the closely allied family of Cytoryctidæ which includes among others the organisms of smallpox, the parasites are similar in a general way but go through a more complicated life cycle. The organisms in this family produce each but a single pansporoblast which is without a membrane, and nuclei are apparently wanting. This family represents the lowest of the Sporozoa and contains several genera; the only one of importance here being Cytoryctes, the cause of variola. As our knowledge is incomplete as yet, it may be proper to depart from the usual form of this article and present a summary of the brilliant researches of Calkins, made in conjunction with the important studies of Councilman and his associates at the Harvard Medical School. The vaccine bodies had been seen and variously interpreted by many observers before the date of Councilman's work; but no clear association in a life cycle of the stages observed had been offered.

Cytoryctes variolæ Guarnieri 1892.—The first development of the organisms in the host is unknown, but probably similar to the known gemmule formation, as Calkins calls it. From the seat of primary infection, these gemmules (schizonts) are probably carried in the blood to the skin where further development takes place. While the foregoing portion of the life cycle is purely conjectural, the subsequent record is fairly complete. The gemmules are here intracellular, cytoplasmic, amœboid organisms which in turn produce similar gemmules. This constitutes the schizogonic or multiplication cycle, or, as Councilman denominates it, the vaccine cycle of the organism. It continues until the gemmules are distributed to all regions of the skin. Ultimately the gemmules develop into forms which penetrate the nuclear membrane and develop into gametocytes (?) of two types, one producing the male gametes, the other the female. The copula (?) becomes a large amœboid organism in which the single pansporoblast originates. These pansporoblasts give rise to primary sporoblasts and the latter to numerous spores. This portion of the life cycle takes place within the nucleus and constitutes the sporogonic or propagative cycle. These spores apparently attack new nuclei and grow into new secondary sporoblasts which give rise to similar spores; this repetition of the sporogonic cycle is in Calkins' opinion a true schizogony and constitutes a second means of auto-infection by which the organism spreads throughout the nuclei and cells of the skin and possibly to other organs of the body. Supposedly it is these spores also which finally transmit the disease to new hosts. The accompanying diagram (Fig. 5200) taken from Calkins' paper will aid in explaining the life cycle just outlined. Every stage represented is reproduced from an actual camera drawing of the parasite and only the tissue cells are drawn diagrammatically.

The parasite is first seen in the skin as a minute cytoplasmic inclusion, 0.5 to 1 μ in diameter. By growth it may reach a size of 10 to 14 μ and from appearances seems to be amœboid. No nucleus, no vacuoles, and no differentiated ectoplasm and endoplasm can be demonstrated. Minute spherical granules are demonstrated by staining and at the close of this stage each lies in a minute vesicle. These are in size and appearance like those at the start of the cycle. After infection of the nucleus and growth a spherical body is produced which resembles a typical cell. It forms but one pansporoblast and grows to a diameter of 10 to 12 μ with

eight to twenty primary sporoblasts developed within it. At first solid and homogeneous, the young sporoblasts become hollow and appear as thickened rings, 1.5 to 2 μ in diameter. After spore formation the sporoblasts are liberated by disintegration of the parent organism. The spore is exceedingly minute (0.5 μ); it develops into the secondary sporoblast. Degeneration of the nucleus and cell leaves the sporoblast in the broken-down material at the bottom of the pustule.

The intranuclear bodies represent the second stage in the life history, which is believed to be the sexual cycle, and produce spores which are the infecting agents. In the opinion of these authors the first cycle may exist without the second, and such is the case in vaccinia.

Apparently these are the same structures seen by L. Pleiffer, Guarnieri, and others, who were not successful

flagella, which by greater length, lesser number, and type of movement are easily distinguishable from cilia. The group shows relationships in many directions, and affords an almost unbroken line of transition to forms which are typically plant organisms. Here, again, as in the last class (Sarcodina), the uniformity of structure, coupled with an even smaller average size and very insufficient acquaintance with the life history, render it difficult to speak positively regarding many of the organisms. Of the sub-classes, which are founded upon the number and arrangement of the flagella, the character of the cell body and general habits of life, only one, Flagellata, is of importance here, as the others contain no parasitic forms.

The general form of the body, the number and position of flagella, and the precise method of reproduction serve to distinguish in the sub-class Flagellata five orders. Only two of these embrace human parasites and demand consideration here, namely: Protomonadina and Polymastigina.

The Protomonadina are small forms, often tending to form colonies. They have at the anterior end one flagellum, two, similar flagella, or two or three dissimilar flagella. In many parasitic species an undulating membrane accompanies a single flagellum. Doflein gives the following key for the determination of those families which include parasitic species:

1. A single flagellum on anterior end 2
Two flagella on anterior end. Bodonidae
2. An undulating membrane along the side of the body. Trypanosomidae
- No undulating membrane present Cercomonadidae

Cercomonas.—The species in this genus are rather uncertain. Many forms have been assigned to it which later studies have shown to belong to other genera. Confusion is possible both with plant organisms and with mere developmental stages of other groups. The species are small and colorless; in form round or oval, with a very large flagellum, which is projected ahead in locomotion. Many of the forms reported from the human body and assigned to

this group are imperfectly known, often found but a single time, and in many cases probably pseudoparasites of various degrees. One or two of the more distinct forms need brief mention here.

Cercomonas hominis Davaine 1854.—Body pyriform, pointed posteriorly, with single flagellum at anterior end. Length 0.01–0.012 mm. Movement rapid, capable of attaching themselves by posterior tip. Smaller variety 0.008 mm. long.

Found in the dejecta of a cholera patient, the smaller variety in typhoid dejecta. Various later reports may be assigned to this species, including that of Lambl in 1875, which has often been erroneously identified as the same as the species described under the same name by this author in 1859. The latter will be discussed under its present name of *Lambli duodenalis*. Some authors have assigned the former species to *Trichomonas*, forgetful of the fact that it possesses but a single flagellum.

It would be hazardous to assert that all typical cercomonads thus far described from the human host fall unquestionably into the limits of a single species; yet in

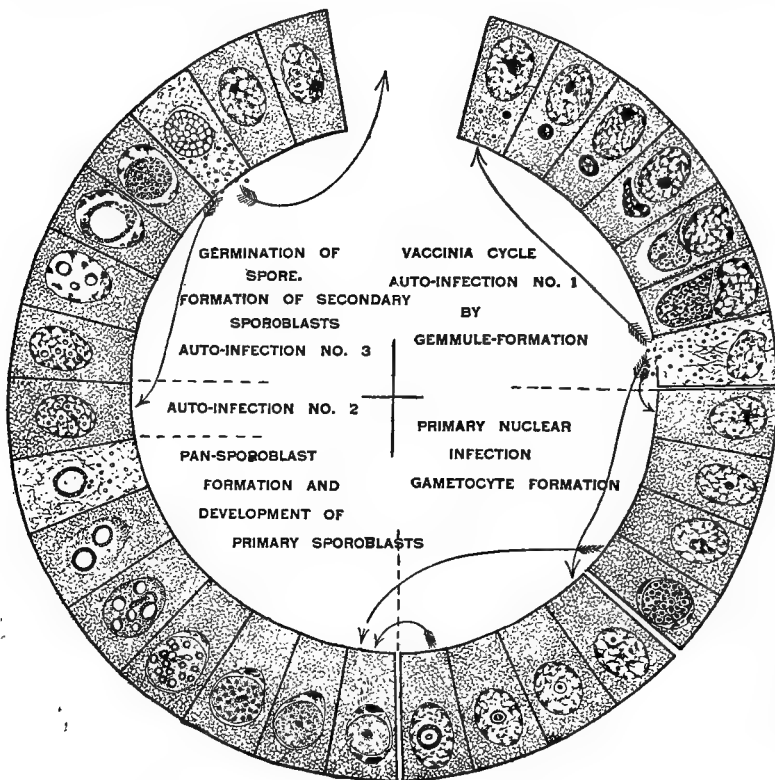


FIG. 5200.—The Variola Cycle of *Cytoryctes variolae* Guarnieri.

in working out the life history as it now stands, although they also did not hesitate to bring them into etiological relation to smallpox. One of the most recent of these (Gorini) has even described and figured both extranuclear and intranuclear bodies in vaccinia. Questionable intranuclear bodies have been reported by several investigators for sarcoma cells in man, but there are also other parasites belonging to this group and affecting lower animals in which an intranuclear existence is well known, e.g., *Eimeria salamandrae* (*Caryophagus salamandrae*), parasitic in the intestinal epithelium of one of the salamanders, and most frequently in the nucleus of the cell parasitized.

In addition to *Neuroryctes* and *Cytoryctes*, Calkins is inclined to include here also *Cyclasterion*, the scarlet fever organism, and finally the still more doubtful organisms of trachoma and molluscum contagiosum which are as yet very imperfectly known and are not discussed in this article.

The class of the Mastigophora includes a great variety of organisms, having in common hardly more than the possession of vibratile organs of locomotion known as

the absence of contradictory evidence they may for practical purposes be considered as such. These forms have been found in the alimentary canal, the bronchial system, in pleural exudate, and in an *Echinococcus* cyst. Encysted forms have also been described. All investigators have not been equally careful to demonstrate the intestinal origin of such forms as were found in faeces, and which may have been due to secondary contamination of the faecal material. Among numerous records only those of Councilman and Lafleur and of Dock concerning the occurrence of such forms in this country need be mentioned. Recently Musgrave refers to it as common in Manila.

Monas pyrophila R. Blanchard 1895. (Syn. *M. pyrophila* Neveu-Lemaire 1902.) Form similar to large spermatozoa, 0.03–0.06 mm. in diameter of body, with long filament from rounded pole, resembling a flagellum, yet capable of retraction when the form becomes nearly spherical. Outside a cuticular (?) layer, which extends through the body in partitions, dividing it into three regions. Movement rapid, accompanied by change of form.

Found by Grimm in sputum and pus of abscesses in lung and liver of patient in Japan.

A diarrhoea caused by monads is recognized by investigators in the Philippine Islands. No detailed account of the form has yet been published.

Herpetomonas.—Elongated rod-like forms with one flagellum at the anterior end and a contractile vacuole at its base. These rather slender and firm-bodied species are found in the alimentary canal of the house fly and other species, including also fleas and mosquitoes. Patton has suggested that the supposed developmental stages of *Trypanosoma* in the louse and flea are really phases in the life cycle of *Herpetomonas* and allied genera. This author has worked out similar conditions for species in other hosts. On account of the evident likelihood of confusion investigations in this field must be particularly carefully carried out. *Herpetomonadine* parasites in tsetse flies and mosquitoes have also been studied by Novy. The former he believes to have been confused with the trypanosomes transmitted by these flies and to have been incorrectly interpreted as stages in the life cycle of the trypanosomes.

Patton also holds that the Leishman-Donovan bodies belong to this genus. The life history of this form is, however, sufficient justification for following Ross in regarding it as a separate genus, even though it be closely related.

Leishmania.—Schizogonic forms round or oval, with nucleus and blepharoplast; intracellular parasites (in endothelial cells?); most numerous in internal organs but appearing at times (ingested?) in leucocytes. Multiplication by longitudinal fission, also by rosettes (a sexual phase?). Schizogonic cycle in warm-blooded host. Flagellated forms developed in cultures at lower temperatures. Sporogony in insects (?). Sporogonic forms unknown. Only two species known, both parasitic in man during schizogonic cycle.

Leishmania Donovanii Ross 1903. (Syn.: *Piroplasma Donovanii* Laveran et Mesnil 1903; *Herpetomonas Donovanii* Rogers 1904.)—Schizogonic form small; ovoid, 2 to 3.5 μ by 1.5 to 2 μ ; protoplasm finely granular and vacuolated; two chromatin masses, the larger a spherical nucleus and the smaller, a bacilliform blepharoplast. These occur in variable numbers in nearly every organ of the body, but especially in the endothelial cells of the blood and lymph vessels, being most abundant in the spleen, bone marrow, and liver. They are also found commonly in leucocytes in the blood where they are most numerous in the later stages of the disease. Examination of the blood in the early stages is of doubtful diagnostic value. The parasites are probably always (?) intracellular, but during the operation of spleen-puncture the cells in which they lie rupture readily so that in smears they often appear free or in clusters like malarial rosettes. The rupture of these cells *intra vitam* must also frequently occur naturally during growth and

thus the organisms will be set free in the blood stream and widely distributed throughout the body. They will also naturally accumulate in the organs already noted above.

In cultures they enlarge rapidly to a diameter of 7 to 9 μ , gradually assuming a pyriform shape which soon becomes flagellated. Such forms carry a single flagellum but no undulating membrane; they measure 12 to 20 μ in length. Sterile blood acidified with a little sodic citrate has been used as the culture medium and is ineffective if held at body temperatures. Some development takes place at 27° C. but 20° to 22° C. appears most suitable. Then the parasites multiply rapidly by longitudinal division. They have been seen to throw off also fine linear forms, comparable to spirochaetes in delicacy. Thus far experimental transmission to vertebrates has been unsuccessful. Efforts to infect mosquitoes, ticks, and lice were also without results, but Patton has recently succeeded in infecting bedbugs and claims to have secured the complete cycle in this host. These experiments need confirmation but there is much indirect evidence which favors the acceptance of the view that the disease is transmitted in some such manner. The long time during which the disease clings to houses indicates that the organism may be transmitted to a second generation of the infecting agents through the ova, as has been established in the case of some other related flagellates.

The parasite is the cause of kala-azar, also known as dum-dum fever or tropical splenomegaly, which is characterized by a high mortality. It is endemic in certain parts of India, especially Assam. Despite the fact that it is not responsive to quinine, it was formerly regarded as a peculiarly bad form of malaria. It also occurs in Ceylon, China, Arabia, Algeria, and Egypt, though previously unrecognized. Rogers has demonstrated that Kala-azar is a house disease. The abandonment and destruction of native houses has proved a valuable though partial prophylactic measure. The annihilation of the bedbug will apparently be much more effective.

The parasites can be demonstrated in the blood in many cases though with difficulty. The organisms should be sought for in the leucocytes. Careful search should be made before the dangerous splenic puncture or somewhat less serious hepatic puncture is undertaken. Smears of spleen or liver pulp are spread, dried, and stained like blood films. Leishman's or Giemsa's methods of staining are recommended.

Leishmania tropica (Wright 1903). (Syn. *Helcosoma tropicum* Wright 1903.)—Schizogonic cycle alone known. Morphologically not differentiated from *L. Donovanii*. Originally discovered by Cunningham in 1885, these bodies were first definitely described by J. H. Wright in 1903. Wright's work has been confirmed by Manson and others. The organisms occur in profusion in the granulation cells from Oriental sore, or Delhi boil, a chronic ulcer, locally endemic in many warm countries. It is common at various points in northern Africa, Asia Minor, and southern Asia as far as India. Manson proclaims it to be a disease of camel-using countries and to occur in both dogs and camels from which it is conveyed to man by flies or other biting insects. Since the life history is entirely unknown, this, as well as the possible alternate cycle in such hosts, is only conjecture.

The specific distinctness between *L. tropica* and *L. Donovanii* may be inferred from their geographical distribution, for kala-azar is unknown, e.g., in the Punjab, where Delhi sore is common. Furthermore, kala-azar is a fatal disease while Oriental sore is eminently benign. It is believed that one attack of the latter confers immunity against further infection, and the Jews in Baghdad at one time practised on their children Oriental sore inoculation. The relation of the two species may be somewhat analogous to that between the organisms of smallpox and vaccinia.

The Trypanosomidae are parasitic forms with a chief flagellum directed anteriorly, usually two-edged, with

more or less of a spiral twist in the body, and with one edge of the body provided with an undulating membrane. The numerous species are hæmatozoa in vertebrates, though some live in the body cavity and alimentary canal of both vertebrates and invertebrates. Those forms of importance here all fall in the genus *Trypanosoma* s. str. Much difference of opinion prevails as to the number of species and their limits. Most of them are very poorly known, although several so-called species were discovered as much as sixty years ago; indeed of no form is even an approximately complete account of the life history at hand. Various species are recognized in various parts of the world as the cause of specific diseases among domesticated animals, which have assumed economic importance of the first rank. The most prominent of these are the following, together with the range and host of each species listed.

Trypanosoma Lewisi, in rats and (?) the hamster, reported from Europe, Asia, Africa, and North America, and causing at times fatal epidemics.

Trypanosoma Brucei, in cattle, horses, mules, and wild animals, gives rise to the *nagana* or tsetse-fly disease in Africa south of the Sahara.

Trypanosoma equiperdum, in horse, ass, and other domesticated species by inoculation, causes *dourine* in the circum-Mediterranean region.

Trypanosoma Evansi, in mammals, especially domestic, where it causes the *surra* in India, China, Burmah, and the Philippines.

Trypanosoma equinum, in horses, causing *mal de caderas* in South America.

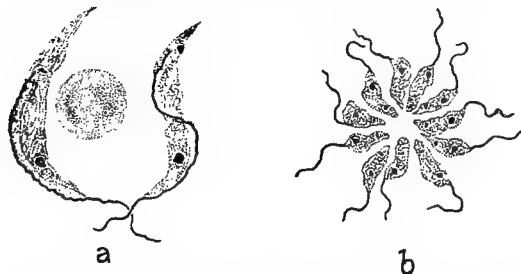


FIG. 5201.—*Trypanosoma Lewisi*. a. Adults with erythrocyte, from stained preparation. $\times 1,000$. b. Multiplication rosette, less highly magnified. (After Francis.)

Trypanosoma Theileri, in cattle, producing the *gal-ziekte* in South Africa.

Although but little evidence is at hand, the weight of opinion is against any possibility of the transmission of these species to man.

Some structural features of the genus *Trypanosoma* s. str. need brief mention. The lancet-shaped body (Fig. 5201, a) shows a finely granular endoplasm and a distinct though very delicate hyaline ectoplasmic layer. The single flagellum arises near the posterior end in connection with the highly refractile granule variously denominated centrosome, micronucleus, and nucleolus. The flagellum continues along the body as the thickened outer margin of the undulating membrane, and projects free from the anterior end of the animal. The prominent nucleus occupies a slightly different position in different species; it is rich in chromatin and stains deeply in prepared specimens.

Three types of reproduction are imperfectly known: a typical longitudinal division, a budding said by Senn to be more common, and a segmentation or multiple division into numerous spores (?) arranged in rosettes (Fig. 5201, b). The rosette formation is regarded by some authors as the result merely of the successive division of an ordinary individual of the species. These rosettes of enormous size, embracing several thousands of individuals, occur characteristically in cultures of *Trypanosoma Lewisi* (Fig. 5202). Such cultures have been recently successfully obtained by McNeal and Novy

in a strictly pure form, and have been maintained for several years. The great importance of this step for the study of the pathogenic activity of the organism and of

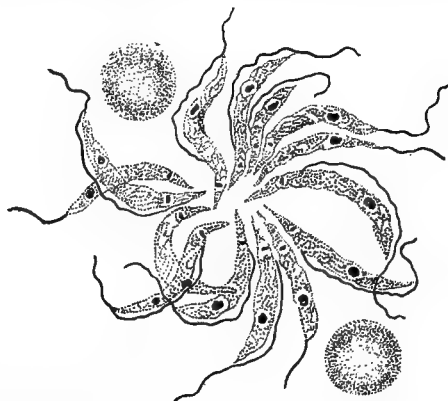


FIG. 5202.—*Trypanosoma Lewisi*. Auto-agglutination. Highly magnified. (After Francis.)

the possible protective measures in combating the disease is evident at once. The species found in man is

Trypanosoma gambiense Dutton, 1902. (Syn.: *T. hominis* 1903; *T. Neveu* Sambon 1903.) Length in stained preparation (Fig. 5203), including flagellum 0.018–0.025 mm., width 0.002–0.0028 mm. Free part of flagellum about one-third of total length. Anterior end attenuated along flagellum, posterior end roughly conical, very blunt. Oval macronucleus just anterior to centre of body, occupying entire width of animal. Near posterior end dark spot, the blepharoplast (the centrosome of Laveran and Mesnil), and just anterior to it a large vacuole well marked. The flagellum ends at the upper edge of this vacuole. The first record of the occurrence of a trypanosome in man is said to have been published by Neveu in 1891, and again in 1898. The description given, however, is too scanty to admit of any opinion regarding its general character, though many are inclined to interpret it as a member of the genus *Trypanosoma*. This species was discovered in 1901 by Dutton in the blood of an Englishman in government employ on the Gambia River. The case was under observation some time, namely, until the patient died in January, 1903, and manifested the following clinical features: general weakness, irregular lapsing fever lasting one to four days with apyrexial periods of two to five days, some cedema, injection of the skin, enlargement of the spleen, constant frequent pulse, and

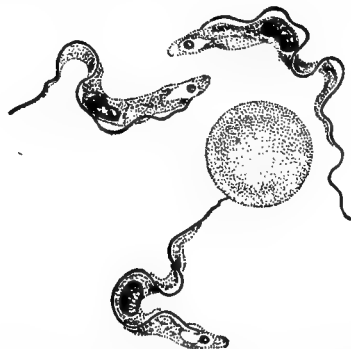


FIG. 5203.—*Trypanosoma gambiense*, with erythrocyte, drawn from stained preparation. \times about 1,900. (After Dutton.)

hurried breathing. These symptoms were associated with no definite organic lesions.

In many prepared slides and fresh blood mounts there were found no malarial organisms. The number of try-

panosomes present varied from one to fifteen, but in apyrexial periods none were detected in the blood. The parasite usually progressed with the flagellum in front, but occasionally reversed direction for a short distance. In slow progression wave-like motions start in the flagellum and are communicated to the undulating membrane; in rapid motion the body rotates on its longitudinal axis so that the undulating membrane appears as if spirally arranged. In one instance a mononuclear leucocyte was observed which had partially engulfed a trypanosome, only the flagellum and a small part of the anterior end of the body remaining free.

In films of blood taken from a child three years old the parasite was discovered again and associated with it malarial organisms. Annett points out that the chronic character of the disease, the rarity of the parasites, their apparent absence at long periods from the peripheral circulation, and the occasional rise in temperature favor confusion with malaria in diagnosis.

Later further cases of the malady have been identified by Dutton, Manson, and others, making in all six cases on the Congo River and seven on the Gambia, which are nearly equally divided between natives and Europeans. It is thus evidently not rare in tropical Africa, as Dutton found his seven cases in somewhat more than one thousand examinations in Senegambia. Two investigators seem to have identified it in India also, and most writers now agree that this trypanosome fever is merely the first stage of sleeping sickness, to be described later.

A related subsequent contribution of great importance to this subject has been made by Castellani, who found *Trypanosoma* in the cerebro-spinal fluid of natives afflicted with the so-called "sleeping sickness." This hitherto entirely unexplained disease, epidemic in certain regions of Africa, attacks only natives, and is characterized by a drowsy condition culminating in deep coma, with an all but universally lethal outcome in from three to twelve months. Hyperæmia of the arachnoid vessels is among the marked pathological features. Bacteriological investigations have remained without result, and the theory of Manson that the cause of the malady lay in the presence of *Filaria perstans* has already been referred to in another article (*Nematoda*). Castellani's hypothesis has been greatly strengthened by the communication of Bruce to the Royal Society that *Trypanosoma* was present in the cerebro-spinal fluid in every one of thirty-eight cases of sleeping sickness investigated in Uganda, and occurred also in the blood in twelve out of thirteen cases tested on this point. A long series of investigations by English, French, German, and Portuguese Royal Commissions has demonstrated beyond question the presence and relation of the organism to the disease, and of the trypanosome fever to sleeping sickness.

The parasite of sleeping sickness which was originally regarded as a separate species, *Trypanosoma Castellani* Sambon, has been shown positively to be the same as the blood-inhabiting form previously discovered, so that only one human trypanosome is known. The invasion of the nervous system marks the transition from the early to the later stage of the disease. The trypanosomes cannot be found in the cerebro-spinal fluid of early cases, but they are always present in the lymph glands in this stage, of which glandular enlargement is a constant and characteristic feature. Dutton and Todd found palpation of the cervical glands the simplest and most accurate means of diagnosing early cases. Sleeping sickness is the last stage of trypanosome infection and in it the parasites may always be detected in the cerebro-spinal fluid.

The trypanosome brings about conspicuous changes in the blood. There is a marked reduction in the number of erythrocytes, which may even fall to one-third the normal number; the leucocytes are increased in number, but there is no eosinophilia. In the blood the distribution of the trypanosomes is very irregular and variable. They occur also in lymph glands and in the testicles.

The parasite is transferred from host to host by the Tsetse fly, *Glossina palpalis*, and perhaps by other species of this genus. According to the views of certain investigators, Bruce, Minchin, and Novy among others, the fly is a mere mechanical vector and the supposed developmental forms in its gut are not developmental stages of the human parasites but merely harmless parasites (*Herpetomonas*) of the fly. Other authors incline to the view that the parasite manifests alternation of generations with the fly as an alternate host. Reports from Koch indicate that he is able to demonstrate this condition. Minchin maintains that both a direct and an indirect transfer take place here as in the dissemination of protozoan blood parasites by biting insects generally. These modes of infection are (a) the inoculative, with developmental changes in the insect, and (b) the contaminative with changes during encystment when the infection of the new host is achieved through contamination of food or drink by cyst-containing excreta. Sambon conjectures a hereditary transmission of this parasite from one tsetse fly to the next generation.

Sleeping sickness is universally fatal in outcome and the former view that the whites enjoyed a racial immunity to the disease has proved to be only a relative freedom from infection due to clothing and habits of life. The severe effects are probably due to a toxin produced by the parasites, and this substance induces profound changes in the nervous tissue so that even the destruction of the parasites is unavailing in the late stages of the disease. In the lymph glands some parasites undergo involution, assuming an ameboid condition, and ultimately perishing. Trypanosomes are also subject to phagocytosis, but possibly only when abnormal or degenerate. These are the forms which accumulate in and block the cerebral capillaries in acute cases.

The parasite and the disease may be transmitted to the chimpanzee and some monkeys in which the disease runs a characteristic human course. Mention should be made of the extensive use of arsenical preparations, especially atoxyl, in the treatment of the disease. Koch and others regard it as specific; but in the opinion of many this conclusion rests on very inadequate data and is controverted by other observations. Much experimental work has been done in chemical therapeutics, with serums and splenic extracts, through ingestion of attenuated cultures and by exposure to various types of rays.

Thus far only three groups of chemicals have been discovered which are efficient in the treatment of trypanosome infections. They are: (a) benzidin dyes, (b) basic triphenyl-methane dyes, and (c) arsenical compounds. In experimental animals complete cure has apparently been effected by maximum doses of these compounds. With lesser doses and prolonged treatment the parasites may disappear from the blood for a time, but later on make their appearance again. Those which recur have undergone a pronounced change in their biological characters and constitute a strain resistant to the therapeutic agent employed. Such a strain manifests chemo-resistance of a specific character toward the particular substance used to develop it and an increased resistance toward other compounds of the same group. On the other hand, the development of resistance toward one group causes no increase whatever in the resistance toward other groups. By continued experiments, however, a strain has been produced manifesting a triple resistance. Chemo-resistance once acquired persists unchanged while the resistant trypanosomes are passed through normal animals even for one hundred and forty transfers extending over fourteen months.

Although the morphological differentiation of the various species of *Trypanosoma* is difficult, not to say impossible at present, there are sufficient grounds in the clinical features of the diseases caused by them, and in other physiological data, such as the immunity of various host species to certain forms, to justify the acceptance of their specific distinctness. One may well recall the

earlier view, that only one form of malarial organism existed, and may find in the transport by *Anopheles* of different species of *Plasmodium* a case parallel to that of the tsetse fly.

Spirochæta.—Body excessively slender, spiral, flattened, ectoplasm forming a narrow undulating membrane which extends in a spiral the length of the body. No flagella, no endogenous spores. Nucleus very elongated, filiform, in the axis of the body, with chromatin granules distributed along its surface. Reproduction by longitudinal division. Type species, *Sp. plicatilis*.

All these forms are by some students assigned to the bacteria. Some species are inhabitants of stagnant waters, others live in decaying organic materials, while still others are parasitic. Among the latter are forms recently recognized as the cause of most virulent infective diseases in man and other animals. The genus was originally characterized by Ehrenberg in 1833 and has been redefined by Blanchard in 1906. No doubt better knowledge will lead to the removal of groups of these species to new genera, but such must be based upon distinctive characteristics; any other basis only results in greater confusion. Apparently the group of forms producing relapsing fevers may justly be made an independent genus even though their morphological differentiation is difficult. New forms are being described constantly, e.g., *Sp. lymphatica*, which White and Proescher regard as the cause of a lymphatic spirillosis; it stains like *Treponema pallidum*. More extended investigation alone will justify assigning a definite place to such organisms.

Spiroschaudinna.—Blood parasites only imperfectly known. In blood of vertebrate host, schizonts are minute, wavy or spiral thread-like bodies, with undulating membrane but no flagella. Free stage alternates with intracellular resting stage with parasite coiled up in host cell. Sporogony in ticks. Stages have been demonstrated in ova, showing the hereditary transmission of the infection. This is contrary to known facts regarding bacteria. Type species, *Spiroschaudinna recurrentis*.

This genus is as yet not clearly differentiated from *Spirochæta* and may ultimately prove to be synonymous with it. Some observers, prominent among whom is Novy, believe these forms to be spirilla and to belong to the bacteria. The question is still *sub judice*, but I incline to the opposite view, held by Schaudinn, Prowazek, Sambon, and others.

Spiroschaudinna recurrentis (Lebert 1874).—(Syn. *Spirochæta recurrentis* Lebert 1874; *Sp. obermeyer* Cohn 1875.) Schizont 7 to 9 μ long by 0.25 to 3 μ broad with two to three turns in the spiral. Shown by Obermeier and others to be the cause of relapsing fever of Europe in man. Common in Russia, Balkan peninsula, Turkey, Persia, and India.

According to Patton, sporogony takes place in the common bedbug (*Acanthia lectularia*). The body louse (*Pediculus vestimenti*) has also been suspected. The evidence is not conclusive.

Spiroschaudinna Duttoni.—(Syn. *Spirochæta Duttoni* Novy and Knapp 1906.) Morphologically difficult to distinguish from *Sp. recurrentis*, although the schizont is said by Novy to be 16 μ long by 0.2 μ in diameter with only two to three turns in the spiral. Shown by Ross and Milne to be the cause of African tick fever, a relapsing fever of man.

According to Dutton and Todd the sporogony takes place in *Ornithodoros moubata* (Murray) and the organism is transmitted hereditarily from the female to the young. Koch demonstrated this spirochæte in the eggs as well as in adult ticks and Carter confirmed these observations. If observed long enough relapses occur in experimental animals. These facts indicate that these organisms are Protozoa rather than bacteria.

There is some evidence which indicates that the relapsing fever of Bombay is apparently due to a different spirochæte from either *Sp. recurrentis* or *Sp. Duttoni*.

Other supposed species have been discovered in the

blood of the domestic goose, in domestic fowls of Brazil, in Transvaal oxen, in Abyssinian sheep. It has been conjectured with considerable probability that the Miana disease of Persia transmitted by *Argas persicus* and other tick diseases in tropical and sub-tropical regions are due to the inoculation of closely related organisms. Thus far the differential technique has not been sufficiently developed or the investigations on individual forms carried far enough to determine the limits of species or the relationships of the different forms which have been reported. New organisms are being brought forward constantly with insufficient data for determining their positions and affinities.

Treponema.—Schizont spiral, delicate, transparent, not flattened but cylindrical in section, with tapering ends. No undulating membrane but a flagellum at each (?) extremity. Multiplication by longitudinal division; the initial stage can be identified by doubling of the flagellum at one extremity and the division forms remain long attached by their ends. Sporogony not known, but so-called sexual forms described. Type species, *Tr. pallidum*.

Treponema pallidum (Schaudinn 1905).—(Syn. *Spirochæta pallida* Schaudinn 1905; *Spirochæta pallidum* Vuillemin 1905; *Microspirochæta pallidum* Stiles and Pfender 1905; *Trypanosoma luis* Krzyszt. and Sied. 1905) Schizont slender, active, length 4 to 14 μ , with ten to twenty curves, narrow, sharp. Sporogony in an alternative invertebrate host unknown; transmission ordinarily, if not always, by direct inoculation in schizogonic stage.

Discovered by Schaudinn and Hoffmann in syphilitic lesions and found by many subsequent investigators in all countries in lesions of both acquired and congenital syphilis; transmitted experimentally to apes with the result of producing characteristic lesions of this disease; sought for in vain in non-syphilitic lesions, this form is now generally recognized as the pathogenic agent in syphilis.

Trypanosoma equiperdum which produces the *mal du coit*, or *dourine*, a disease of horses analogous to syphilis, is like *Treponema pallidum* in being transmitted ordinarily by contact, whereas allied species pass through another host if not another cycle in that as intermediate host. Some evidence indicates the possible transmission of dourine by a biting insect, and thus suggests the former existence in the *Treponema* life cycle of another host and of a now generally lost cycle of development peculiar to that host.

Treponema pertenue Castellani 1905.—(Syn. *Spirochæta pertenue* Castellani 1905; *Sp. pallidula* Castellani 1905.) Length of schizont up to 20 μ , turns uniform, narrow and numerous; morphologically very similar to *Tr. pallidum*, though apparently more delicate and with narrower waves.

Probable cause of yaws (frambæsia) in the lesions of which it occurs regularly. It also occurs in glands but not in blood, urine, or cerebro-spinal fluid in such cases.

That some other spirochætes should be transferred to this genus can hardly be doubted, but this depends on the demonstration for them of morphological characters which conform to the definition of this genus.

The family of the Bodonidæ would not call for any discussion here were it not for the frequency with which certain species have been assigned a rôle as parasites of man. The form which has most frequently been mentioned in this connection is

Cystomonas urinaria (Künstler 1883).—(Syn.: *Bodo*



FIG. 5204.—*Cystomonas urinaria*. Magnified. (From Braun, after Künstler.)

urinarius Künstler 1883; *Cystomonas urinaria* Blanchard 1886; *Plagiomonas urinaria* Künstler of Braun 1895.) Shaped like a beet root (Fig. 5204), 0.01 mm. long, 0.004–

0.005 mm. broad, the broad anterior end notched, the posterior end in the form of a long slender filament. Nucleus anterior; two similar flagella originate from anterior notch.

In 1856 Hassall described an infusorian which he had observed in alkaline urine that had stood some time open to the air. It was subsequently found in fifty samples of urine from various sources left open similarly, sufficient proof of the contamination. In 1883, however, K nstler reported a form under the same name from fresh urine, which was accordingly attributed to the urinary passages. Blanchard held this to be in reality a new species and renamed it, bringing it in connection with a form described by Salisbury as *Trichomonas irregularis*. Braun regards the latter as rather *Tr. vaginalis*, and distinct from the former, for which he inclines to the view that it was actually a contamination. This is the more probable, as Th. Barrois found many flagellates in "freshly voided" urine in Lille, when subsequent examination yielded no trace of these parasites in urine of the same patients. Evidently the presence of such forms in human urine is beyond question, but their origin from the human urinary passages is yet to be demonstrated. That all such cases require the most searching examination is evinced by a recent experience of my own, in finding objects which were probably much contracted rotifers in preparations made from "absolutely fresh" urine.

The order Polymastigina includes small forms, always non-colonial, with three similar flagella, or with four to eight flagella dissimilar in size and differently located. Two families contain parasitic forms and are distinguished as follows:

Body with three or four flagella, all at the anterior end Tetramitid 

Body with four to six flagella on anterior end; posterior end either with two flagella, or prolonged into one to three lobes. Polymastigid 

In the Tetramitid  are included species of elongated form with usually pointed posterior end. They have no cuticula, or pellicle, hence may also manifest amoeboid movements. One of the flagella may be represented by an undulating membrane. Only one of the genera, *Trichomonas*, embraces human parasites. The diagnosis of the genus may be given briefly as follows:

Trichomonas Donn .—Generally pyriform, with anterior end rounded or almost pointed. Posterior end moderately pointed. Nucleus near anterior end, vacuoles near posterior, no contractile vacuole. Either three equal flagella from anterior tip, and also an undulating membrane (*Trichomonas* s. str.), or with three equal flagella directed anteriorly, and one much longer extending posteriorly from the same point of insertion (subgenus *Trichomastix*).

Trichomonas vaginalis Donn  1837.—Body very mobile, usually pyriform or spindle-shaped (Fig. 5205), with

other investigators) of equal length, and an undulating membrane which winds spirally about the body to the base of the posterior tip. Plasma finely granular, nucleus near anterior end; posterior to it according to Blochman two longitudinal rows of prominent granules. Division has been reported; encystment is as yet unobserved.

This species is present in females where vaginal catarrh is associated with an acid reaction of the secretion. It has been found in girls of six or seven years and in aged women; and other conditions affect its presence as little as age save that menstruation, alkaline injections, or other conditions which alter the reaction of mucus result in its disappearance temporarily at least. A low temperature (15  C. or less) is also fatal to its existence. Dock and others have demonstrated the presence of this species in the urine of males; the infection doubtless resulted from intercourse and was made possible by an already abnormal condition of the male urethra, as was shown in the cases under discussion. Dock was unsuccessful in infecting guinea-pigs and dogs, and the means of transference from one female to another is unknown. According to Hausmann thirty to forty per cent. of females are infected. The parasites are easily demonstrated in the vaginal mucus, where they move slowly about among epithelial fragments and mucous corpuscles; but for successful demonstration the urine must be examined as soon as passed. Whether their relation to the vaginal catarrh is primary or secondary remains entirely undecided.

Trichomonas intestinalis * (R. Leuckart 1879).—(Syn.: *Protoryxomyces coprinarius* Cunningham 1881; *Monocercomonas hominis* Grassi 1882; *Cim nomonas hominis* Grassi 1882; *Trichomonas hominis* Grassi 1888; *Cercomonas coli hominis* May 1891; *Monocercomonas hominis* Epstein 1893.)

Very similar to *Tr. vaginalis* but smaller, measuring 0.004–0.015 mm. in length and 0.003–0.004 mm. in breadth, without rows of granules; posterior end more sharply set off and measuring only one-third the length of the body. Three flagella, the free edge of the undulating membrane has sometimes been interpreted as a fourth. Otherwise as in *Tr. vaginalis*, although the species has not been carefully investigated. Kruse and Pasquale observed groups of individuals which may have arisen by division. Before copulation this species loses its flagella and creeps about with bluntly lobose pseudopodia. This species is ordinarily identified as the *Cercomonas hominis* of Davaine (1854) and the *C. intestinalis* of Lambl (1875), but recent studies have demonstrated the individuality of this from the two cited. There also is a tendency at present to reduce this form to *Tr. vaginalis*, with which it agrees closely, and only an exact study can decide the question. In the uncertainty I regard it as more practical to retain both species, though they are at least closely related.

Tr. intestinalis parasitizes in the anterior and middle regions of the human alimentary canal, and has been repeatedly found in various parts of the world. It occurs also in the oral cavity in decaying teeth, where it nourishes itself on micrococci. It has been reported also frequently from diseased conditions associated with diarrhoea, such as typhoid, cholera, intestinal catarrh, gastric carcinoma, and once in pulmonary gangrene. The species lives only in fluids of an alkaline reaction. Its occurrence in the dejecta of healthy adults has been taken to indicate a commensal rather than a parasitic habit; but it at least rapidly multiplies in connection with morbid processes, and this may exercise an important influence on the progress of the disease. An etiological significance cannot, in the present state of knowledge, be attributed to this species; yet the experiments of Epstein showed that an infection is apparently produced by drinking-water and followed by diarrhoea in children. Experimental infection of animals has not

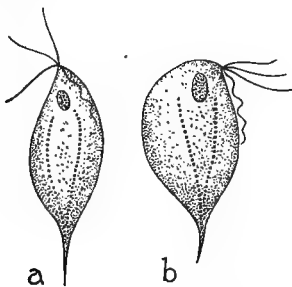


FIG. 5205.—*Trichomonas vaginalis*. a, From osmic-acid preparation; b, Living. Magnified. (After Blochmann.)

posterior end sharply pointed and anterior end more or less rounded. The posterior tip is half as long as the rest of the body. Total length 0.015–0.025 mm. At anterior pole originate three flagella (four according to

* This form of name is probably incorrect, but as the synonymy is badly confused I have retained it pending revision by some specialist.

divisions of the Sporozoa; the multiplicative reproduction varies often widely among closely related forms.

The two sub-classes, Telosporidia and Neosporidia, are distinguished by the fact that the former produce spores only at the close of the vegetative period, while the latter do so during the entire period. For the identification of a sporozoon a vegetative stage is rarely sufficient; the form and number of the spores produced during the propagative period of reproduction are characteristic.

In the sub-class Telosporidia one may distinguish two orders on the basis of the habit of the parasites and the mode of fertilization which prevails. Thus in the Coccidiomorpha the vegetative stage is permanently intracellular, while the sexual generation may be so only transiently. The fertilization is anisogamous, *i.e.*, by fusion of differently formed gametes. In the Gregarinida on the other hand, the vegetative stage is intracellular only at the start, as the adult organism is extracellular and the sexual generation also. The fertilization is isogamous, *i.e.*, by fusion of equal and similar gametes. Under the order of the Coccidiomorpha are included forms which until recently have been treated as much more distinct. But more careful study, particularly of the life history, has shown an increasing degree of likeness until they are now included in the same order, and mutually opposed to the Gregarinida in the specific cell parasitism, and in a similar alternation of generations and of hosts in addition to the features pointed out in the outline of the system given above. The features which serve to distinguish the two sub-orders of the Coccidiomorpha are these: The Coccidia produce sporozoites encased in sporocysts; with the exception of *Legerella*, the copula is non-motile and remains in the cell. In the Hæmosporidia the sporozoites are always free, the copula is an active ookinet, and migrates to a new location before undergoing further development.

The adult Coccidia occur as parasites in epithelial cells, particularly of the alimentary canal and its adnexa, though the excretory organs, the male sexual organs, and most recently the spleen are also reported as affected. While the protoplasm of the host cell is ordinarily the seat of the parasite, there are not wanting such as occur in the nucleus itself. Only rarely is more than a single parasite found in an epithelial cell.

In form the Coccidia are uniform and constant, being spherical, oval, or elliptical, and without organs of locomotion of any sort or organs of attachment. Their size is regularly insignificant. A noteworthy characteristic is the absence of differentiation into ectoplasm and endoplasm. The plasma of the cell is finely granular, alveolar, and without reserve bodies or food vacuoles. The nucleus is large, vesicular, and characterized by a single prominent central nucleolus. No contractile vacuole is present, and no further structural differentiations can be noted. The cell and nucleus increase gradually in size at the expense of the host cell, which ultimately in most cases degenerates to a mere empty membrane encircling the coccidium.

The nucleus of the now full-grown parasite undergoes multiple division, the protoplasm arranges itself in individual masses about the many daughter nuclei, and



FIG. 5208.—*Eimeria Stiedæ*, Adult Schizont. Completely Divided into Merozoites. Cyst formed of degenerated host cell is not represented. Magnified. (After Simond.)

there results a stage in which a rosette of young forms (Fig. 5208) encircles a central portion of protoplasm, known as the reliquary body or residual mass. This is without nuclear matter and destined to play no further

part. It is left behind, and perishes when the young forms wander out to infect new epithelial cells of the same host, and repeat the process just sketched. This is evidently the multiplicative reproduction already referred to. It serves to effect the auto-infection of the host, and is generally known as the period of asexual

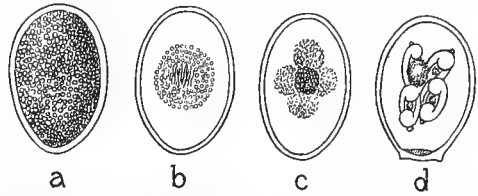


FIG. 5209.—*Eimeria hominis*, Sporogony. a, b, Oocyst; c, sporoblasts with residual mass; d, sporocysts with contained sporozoites. Magnified. (From Braun after Riek.)

reproduction or schizogony. The cell parasites which undergo these changes are schizonts, while the young forms are denominated merozoites. The merozoites are capable of active movements by contraction and twistings, or with a gliding movement, in which a trail of mucus is left behind. The growth of merozoites to schizonts in the epithelial cells, the production of new merozoites, and the infection of new cells proceed often with considerable rapidity, but only within certain limits, for a new type of reproduction intervenes.

In this which regularly begins under the pressure of excessive infection of the host, the merozoites develop not to schizonts, but to forms of two sorts, which at first sight are very similar to schizonts, and but little different from each other. The one form is opaque with a richly granular plasma; the other has a clear but dense plasma. The opaque form is the female gamete, or macrogamete, and attains maturity by the rejection of a portion of its nuclear substance. The clear cell, known as a microgametocyte, undergoes multiple nuclear division. The many nuclei produced then migrate to the surface, each collects a small part of the plasma about itself, and projects as an elongated spindle-shaped structure, the microgamete or male cell, which becomes free, forms two flagella, and enters upon active locomotion. The major portion of the microgametocyte is abandoned, and subserves no further function.

The microgametes swarm about the macrogametes, and as soon as one has succeeded in entering, the macrogamete forms at once a firm membrane, which forbids entrance to other microgametes. The two nuclei unite and the act of fertilization is completed. The product is known as an oocyst, copula, or sporont, and forms the starting-point of a new period in the life cycle, which is that previously designated as the propagative reproduction. It is also known as the sexual spore-forming period, or sporogony, and in most coccidia takes place outside of the host, after the oocyst has been evacuated in feces or urine. The steps in the process of sporogony may be outlined next in general terms (Fig. 5209).

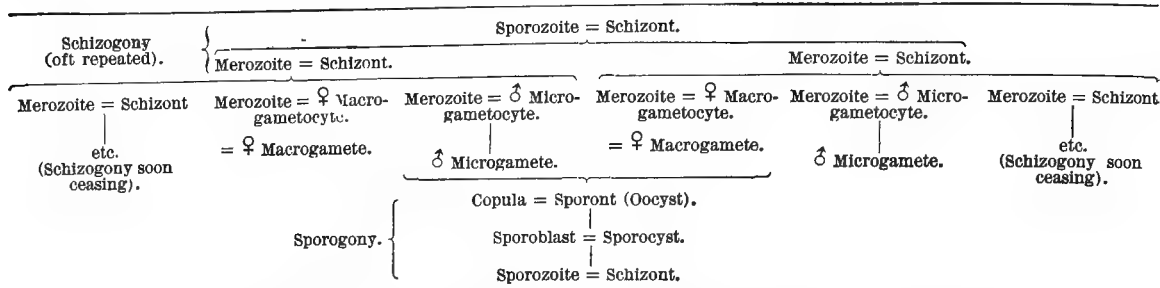
The nucleus of the oocyst (a) divides twice, and about the four daughter nuclei the protoplasm separates into four parts known as sporoblasts (b), and sometimes also a residual mass of protoplasm (c). Each of these sporoblasts surrounds itself with a firm membrane and becomes a sporocyst (d), while later within each sporocyst after nuclear division two sporozoites are formed and a residual mass of protoplasm is left unused. The sporozoites are characteristically sickle-shaped or crescentic, and abandon the sporocyst when this reaches the alimentary canal of the new host, and is opened by the action of the alimentary secretions. The entrance of the sporozoites into the epithelial cells and their growth to schizonts completes the life cycle.

This typical course of development is well represented by the tabular outline given by Lühe and reproduced here. The stages connected by a single vertical line (!) are successive generations in the life cycle; those con-

nected by the sign of equality (=) are produced by growth or metamorphosis within the single generation.

2. Oocyst oval, 33–49 μ by 16–28 μ ; sporocyst spindle-shaped (rabbit, man).....*E. Stiedæ* (Lind.)

DEVELOPMENT OF EIMERIA.



This general plan of development is modified in the individual species in various manner. The most striking modification is a simplification by suppression of the entire schizogonic cycle, so that the macrogametes and microgametocytes arise directly from the sporozoites which have penetrated epithelial cells.

The coccidia parasitize almost all groups of the animal kingdom, and are distributed over the entire world, although, as might be expected, the majority of reports thus far made concerning their presence come from European countries.

For the subdivision of the group Léger's proposal to use the number and form of the sporocysts and of the sporozoites has been generally adopted. The adjoined table gives a review of the common genera arranged according to Léger's scheme.

2. Oocyst spherical or cylindrical, 15–32 μ by 11–17 μ ; sporocyst oval (mouse).....*E. falciformis* (Schuberg)
3. Simple forms. Oocyst oval to cylindrical, 24–35 μ by 13–20 μ*E. hominis* (Riv.)
3. Twin forms.....*E. bigemina* (Stiles)
Eimeria Stiedæ (Lindemann 1865).—(Syn.: *Monocystis Stiedæ* Lindemann 1865; *Psorospermium cuniculi* Rivolta 1878; *Coccidium oviforme* Leuckart 1879; *C. cuniculi* Raillet 1893; *Pfeifferia princeps* Labbé 1896; *Pfeifferella princeps* Labbé 1899. *Eimeria cuniculi* Lühe 1902.)

All stages are known. Oocyst (Fig. 5210) in the liver of rabbit, oval 0.033–0.049 mm. long, 0.015–0.028 mm. broad. Cyst wall heavy, smooth, with opening at one pole. The coarsely granular protoplasm completely fills the cyst, but later contracts to a spherical mass at the centre (0.017 mm. in diameter). Spore formation out-

Ripe oocyst contains	Numerous sporozoites	No sporocysts.	ASPOROCYSTIDEA	Legerella.
		Many sporocysts each with	POLYSPOROCYSTIDEA	Barroussia.
	Eight sporozoites	Two sporocysts each with four sporozoites.	DISPOROCYSTIDEA	Adelea.
		Four sporocysts each with two sporozoites.	TETRASPOROCYSTIDEA	Eucoccidium.
	Four sporozoites	Two sporocysts each with two sporozoites.		Klossia.
				Isospora.
				Eimeria.
				Cyclospora.

Some confusion has prevailed regarding the correct names of the various genera. The original cause of this difficulty rests on the fact that the two phases of the life cycle, schizogony and sporogony, were discovered and named separately, and that their relations as parts of the development of a single species did not become known until a much later date. All of the human parasites thus far recorded from this group fall within the limits of a genus named *Coccidium* by R. Leuckart in 1879, and this name has been generally incorporated into works on the subject. At a very recent date, however, Stiles and Lühe have independently called attention to the fact that the name *Eimeria*, introduced in 1875 by Aimé Schneider, has the right of priority, and must replace the more common form according to laws of zoological nomenclature. This is really fortunate from the general standpoint since the name coccidia has been very generally used for the entire group as well as heretofore for the genus; yet this is not in the interest of precision, and may evidently lead to serious misunderstanding. Henceforth the name coccidia can be used only in the more general sense.

The genus *Eimeria* is the best known of all. Its most important characteristic is the formation in each oocyst of four sporocysts, each with two sporozoites. A residual mass of protoplasm is always present in the sporocyst with the sporozoites, and a similar residual mass is sometimes formed in the oocyst with the growth of the sporoblasts. Of the many species assigned to this genus, the most important and better known forms which are pathogenic to man and some domestic animals are included in the following key:

1. Oocyst with residual mass..... 2
1. Oocyst without residual mass..... 3

side the host requires two to three weeks. The entire sphere divides into four sporocysts each with a thick covering and with a length of 0.012 to 0.015 mm. and a breadth of 0.007 mm. Two comma-shaped sporozoites are formed in each sporocyst, and a granular residual mass of protoplasm lies in the hollow between their enlarged ends (Fig. 5211). The sporozoites are set free by gastric digestion. They ascend the gall ducts, penetrate the epithelial cells, and when fully grown measure 0.02–0.05 mm. in length by 0.02–0.039 mm. breadth. They divide into from 30 to 200 merozoites (Fig. 5208) which spread the infection. Ultimately the formation of ma-

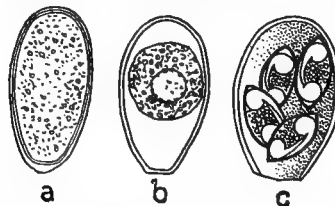


FIG. 5210.—*Eimeria Stiedæ*. Sporogony from Liver of Rabbit. a, Young oocyst; b, same with protoplasm contracted preparatory to division; c, same divided into four sporocysts, each containing two sporozoites which have already developed. Magnified. (a, b, after Leuckart; c, after Simond.)

cro- and microgametes leads to the fertilized sporont stage, the oocyst.

This species is an abundant parasite of the rabbit, in which it parasitizes in the epithelium of gall ducts and liver. According to the degree of infection sooner or

later inflammation and proliferation of the epithelium lead to the formation of nodules of caseous matter, containing amid various remnants coccidia in all stages of development. These conditions may lead to severe

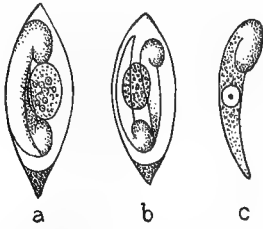


FIG. 5211.—*Eimeria Stiedae*. a, b, Sporocysts each with two sporozoites and residual mass; c, a single sporozoite. Highly magnified. (From Railliet, after Balbiani.)

sickness or even to the death of the host; in other cases the animal recovers, as the process of schizogony appears to have distinct self-limitations. The infection is spread by the contamination of food with spore-infected faeces.

Several cases of human infection are on record. Evidently conditions favor such infection only rarely. To the four positive cases cited by Leuckart, all in Germany and Austria, Silcock has added another from London. A number of doubtful cases are also included here by some authorities. The observation of Thomas in Boston, according to which this species was found in a small cerebral tumor surrounded by bone tissue, has little to support the diagnosis in view of the normal condition of the liver and intestine, and has been universally questioned by reviewers. In any event the supposed coccidia cannot belong to this species, or any other yet reported from man, on account of their size (0.014–0.022 mm. in length). They correspond, however, in size nearly to the coccidia reported by Stiles from sheep, which belong to a species as yet unnamed. More probably they are not coccidia at all.

Eimeria hominis (Riv. 1878), nec. R. Blanchard 1895. —[Syn.: *Cytospermium hominis* Rivolta 1878; *Coccidium perforans* R. Leuckart 1879; *C. hominis* Railliet 1893; *Pjeifferella princeps* (Labbé 1899) in part.]

Oocyst (Fig. 5209) 0.024–0.026, or even 0.035 mm. long by 0.0128–0.014 or even 0.02 mm. broad, plumper than those of *E. Stiedae*, from which also they differ in the constant presence in sporulation of a residual mass of protoplasm that is said to be constantly absent in the latter species. (Compare Figs. 5209 and 5210.) Here also only three to four days are necessary to bring the division of the contents of the oocyst into sporoblasts (sporocysts).

This species, which is so closely related to *E. Stiedae* that many authors regard them as identical, parasitizes

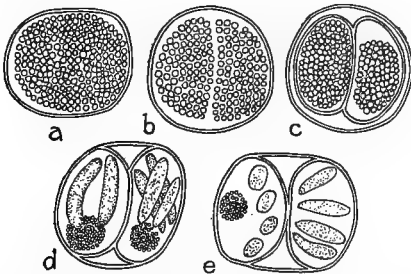


FIG. 5212.—*Eimeria bigemina*. Sporogony. a, b, c, Division into two masses; d, e, formation of sporoblasts with residual mass. Highly magnified. (After Stiles.)

in the intestinal epithelium of the rabbit, where it evokes serious, often fatal epidemics. Railliet and Lucet have demonstrated that infection takes place by the ingestion of ripe spores, and rapid schizogony brings about in a

few days serious auto-infection involving the epithelium and Lieberkühn's glands so as to occlude the latter. The forms found in horse, goat, cattle, sheep, pig, and other wild species are usually regarded as varieties, but the considerable differences in form and size make it more probable that some at least represent distinct species.

Eimer found in two bodies examined in Berlin the epithelium of the intestine filled with coccidia, and even in large part destroyed by them. These are probably referable to this species. Other authors have reported the discovery of coccidia in human faeces at various times without furnishing data for the determination of the species concerned.

Eimeria bigemina (Stiles 1891).—(Syn.: *Cytospermium villorum intestinalium canis et felis* Rivolta 1874; *Coccidium bigemium* Stiles 1891.)

Oocyst (Fig. 5212) 0.012–0.015 mm. by 0.007–0.01 mm. (in dog), or 0.008–0.01 mm. by 0.007–0.009 mm. (in cat), or 0.008–0.012 by 0.006–0.008 mm. (in polecat). The oocyst divides into two parts, each of which encysts and forms four sporocysts. The oocysts occur not in the epithelium, but in the central tissue of intestinal villi (Fig. 5213).

The species was first seen as early as 1854 by Fink, who, however, misinterpreted the character of the objects. It has often been confused with *E. hominis*, from which the above characteristics easily distinguish it. A case of human infection, published by Virchow in 1860, and another by Grunow in 1901, very probably belong here. The description given by Railliet and Lucet of



FIG. 5213.—*Eimeria bigemina* in Transsection of Villus from Intestine of Dog. Highly magnified. (After Stiles.)

coccidia discovered in the faeces of a mother and child who had long suffered from chronic diarrhoea corresponds well with this species in the small size of the bodies found, and is also probably referable to it. The form is evidently only an occasional parasite of man, and infection probably results from lack of cleanliness or too intimate association with pet dogs or cats. It may be that the forms discussed as varieties from different hosts actually represent different species. Stiles has found this species in dogs killed in Washington, D. C.

In 1906 Bancroft and Cross recorded its occurrence in dogs at Baltimore and gave further details regarding the structure of the parasite.

It is not surprising in view of the imperfect acquaintance with this group that all sorts of questionable structures should be referred to it. They are all such as have been reported from man usually in connection with some abnormal condition, and frequently also on the basis of a single occurrence. In most cases only scanty data are given concerning the supposed coccidia, and even of the best known of these problematic structures too little can be said to determine their true nature or position in the zoological scheme. It is best to call attention to certain of these cases briefly, in order that if possible further data should be accumulated to elucidate their real character.

The form known as *Coccidioides immutis* Rixford and Gilchrist, doubtfully included here in the first edition of this work, has been shown by more recent studies on later cases to be in reality a species of *Oidium*. For further details see *Jour. Med. Research*, 1904, 1905.

There are other reports of less definiteness than those just considered, and some of the questionable structures noted therein have found an explanation within recent

times. Thus the psorospermcyts of Lubarsch and Ribbert, which were supposed to play a part in diseases of the urinary passages, are in reality metamorphosed nests of epithelial cells normally found in the urethra. The structures found by Künstler and Pitres in pleural exudate and interpreted by Blanchard as a sporozoon, *Eimeria hominis* R. Blanchard 1895, I have preferred to interpret as *Echinorhynchus* eggs (Cf. *Nematoda*, page 225). More uncertain still are Severi's "monocystic gregarines" from the lung parenchyma of a still-born child.

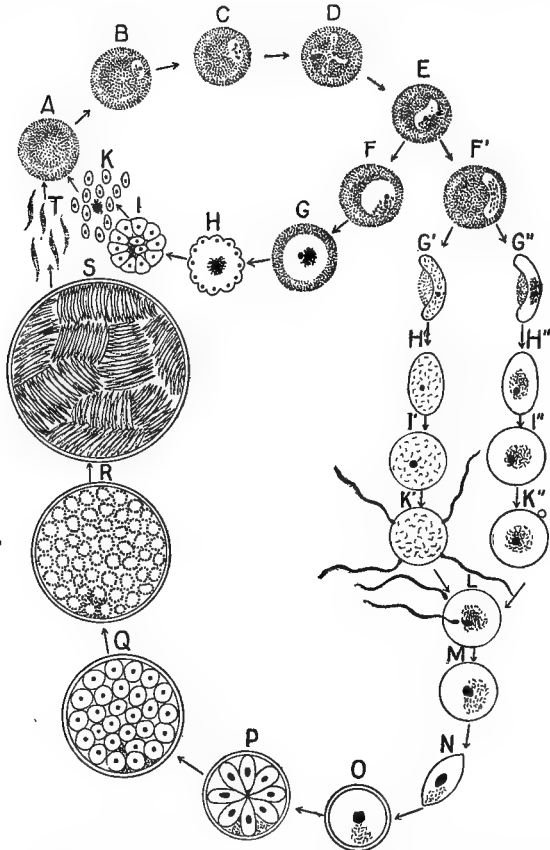


Fig. 5214.—Development of *Plasmodium falciparum*. A, E, G, K, Schizogony in human blood; F', L, formation of gametes and fusion of same; M, S, T, sporogony in mosquito. Somewhat diagrammatic. For further details see text. (After Neveu-Lemaire.)

They are described as oval in form, exceedingly variable in size (0.003–0.03 by 0.0015–0.015 mm.), covered by a thin membrane, and either free or in epithelial cells; it is difficult to interpret them in any satisfactory manner. Some of these doubtful structures are discussed as appendices to the next sub-order, the Hæmosporidia, to which they show a certain similarity.

An error of the reverse type is that frequently made in the past of diagnosing eggs of parasites as coccidia. Thus nematode eggs have once been reported as coccidia, and eggs of trematodes many things. Were it not for the extremely small size of the structures described, the case of J. J. Thomas, noted above, concerning coccidia in a brain tumor would find its easy explanation in this same manner.

The *Hæmosporidia*, like the Coccidia, are characteristic cell parasites. The period of schizogony or multiplicative reproduction is passed in the blood cells, and only very exceptionally in the cells of other organs. These stages have long been known, and with them a few preparatory stages to the sporogonic cycle, although the latter have been entirely incorrectly interpreted as degenerative changes, etc. So far as is known this sporogonic

cycle takes place only in the body of another host; and for the Hæmosporidia of mammals and birds this host is a blood-sucking insect in which the process of sporogony is carried out in the wall of the alimentary canal, and the sporozoites collect in the salivary glands, whence they are injected by the act of biting into a new host to start anew the schizogonic cycle. The close relationship of these forms to coccidia is evident from a study of the life history, as Doflein indicates most aptly in calling them coccidia adapted to parasitism in the blood system.

The life history may be outlined from that of the æstivo-autumnal parasite (Fig. 5214). The earliest stage of the parasite which occurs in the erythrocytes is a minute ameboid body (A) which increases rapidly in size, manifesting considerable ameboid activity (B–E). In connection with the growth of the organism particles of a black pigment matter, named melanin, are stored up in its protoplasm (F, G). The nucleus of the parasite, at first single, begins to divide rapidly when the organism has reached its maximum size and the daughter nuclei collect about the rim of the organism (H). Radial lines of division appear in the protoplasm (I), and the whole falls into a group of young germs or merozoites (K) about a central residual mass of protoplasm loaded with the pigment already referred to. The merozoites infect new blood cells, and the process of schizogony is repeated until conditions, as yet unknown, bring in a new set of changes, the starting-point of another cycle, the sexual phase, or sporogony.

The merozoites develop to individuals differently formed from the schizonts and of two sorts, the one finely granular and opaque (G''), the other hyaline in appearance with a few conspicuous pigment granules (G'). These forms are shaped like a bean in the species under consideration, and are those previously designated as half-moon or crescentic bodies. When fully grown they desert the corpuscle (H', H'') assume a spherical form (I', I''). The macrogamete extrudes a portion of the nuclear substance (K'') and is mature. The nucleus of the microgametocyte divides, the parts migrate to the surface and form microgametes by a small accumulation of plasma about each (K'), leaving a large central residual mass. These two gametes copulate, their nuclei fuse, and the product (M) is the starting-point of the sporogonic cycle, the sporont.

The changes leading to the perfection of the sexual cells take place only after the blood has been drawn into the stomach of the new host, the blood-sucking insect. Abnormal stimuli may, however, bring about some of the changes, as in cultures of malarial blood. The copula acquires an ameboid form (N) necessary for its attainment of a location within the tissue of the new host. This motile stage, which has been denominated the ookinet, is a gregarine-like organism, and penetrates an epithelial cell, where it transforms itself into an immobile spherical oocyst (O). After nuclear division there are formed in the oocyst numerous sporoblasts (P, Q), which, however, never acquire a heavy membrane, i.e., never become sporocysts as in the coccidia. Each sporoblast gives rise to a large number of sporozoites (R, S), which are set free into the body cavity of the insect host by the rupture of the wall of the oocyst. They collect as the result of an evident chemotactic influence in the salivary gland, and are injected into a new host when the insect bites. There they enter the erythrocytes and the life cycle begins anew.

The organisms included in this sub-order are the cause of serious diseases, and their number is being rapidly increased by the investigations of most recent times. Many doubtful forms have also been placed temporarily under this heading, so that it is impossible to give a synopsis of the genera, or to fix the precise limits of the sub-order itself.

Most prominent of the forms which are included here are the parasites of human malaria. Grassi still regards these all as merely varieties of one species. This is clearly doing violence to the ordinary zoological significance of the word. On the other hand, several investigators

have grouped them into two genera, a plan which I myself followed in an earlier paper. Here they will be treated as three species of one genus in accord with a recently expressed view of Schaudinn, and with the known facts regarding their clinical manifestations, structural differences, and life histories.

The genus *Plasmodium* includes in addition to these species the parasite of avian malaria also. It was established in 1885 by Marchiafava and Celli, and although the name is employed here in a sense utterly at variance with its meaning as a term in general scientific use, yet the rules of zoological nomenclature call for its retention. The malarial organism was first seen and figured by Klencke in 1843 without any idea of the significance of the structures viewed. Laveran in 1880 was the first to attach etiological significance to the structures he described from the erythrocytes in cases of malaria. A large number of investigators participated in the gradual elucidation of the schizogony of these parasites. It was 1896, however, before Manson set forth distinctly the agency of the mosquito in transmitting the disease. Just a year later Ross actually followed for the first time the fate of the parasites of avian malaria in the mosquito's stomach, and their development up to the infection of a new host by the sporozoites. Ross' observations on avian malaria were confirmed soon after by Grassi and other Italian investigators for human species of the malarial parasite.

The complicated terminology in this group, due to the continual changes introduced by various investigators, renders it advisable to give here for general information the table prepared with such success by Lühe, which shows the correspondence in the nomenclature of the chief investigators of recent date. The terminology of Schaudinn, which is followed in this article, has been more generally adopted than any other, and has much in favor of it from every standpoint. (See table below.)

Young form in erythrocyte small, unpigmented; movement slow; pigment in coarse granules, first visible in about twenty-four hours, and peripheral in position. Movement decreasing until in sixty hours after the attack, or twelve hours before the next, the spherical *Plasmodia* fill almost the entire corpuscle. Having reached a diameter of about 0.007 mm. schizogony begins, and nine to twelve (rarely six to fourteen) merozoites are formed which are very regular (Fig. 5215, e). The me-

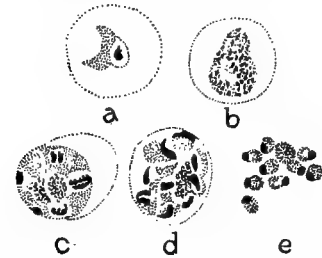


Fig. 5215.—*Plasmodium malariae*, Schizogony. a, b, Growth of schizont; c, nuclear division; d, formation of merozoites; e, release of same by destruction of erythrocyte, residual mass at upper side of group. Magnified. (After Bastianelli and Bignami.)

lanin granules move in radial lines and collect in the central residual mass, from which the merozoites separate themselves in seventy-two hours. The synchronous release of these germs brings another paroxysm at this time, whence the name of quartan fever for the disease induced by this species, which is also often designated the quartan parasite. The gametes are few in number, spherical, and characterized by active streaming in the protoplasm. The sporogony of this species in *Anopheles* goes on at a minimum of 16.5° C., and

Schaudinn, 1899 and Lühe, 1900.	Ross, 1898.	Ross, 1899 and 1900.	Ray Lankester, 1900.	Harvey Gibson, 1900.	Koch, 1899.	Grassi, 1898-1899.	Grassi, 1900.
Schizogony					Endogenous development.	Sporulation (fase asporulare).	Monogonia (generazione neutrale) per sporogonia conitomica.
Schizont	Sporulating form.	Sporocyst (young form: amebula s. myxopod)	Oudeterospore		Full grown parasite.	Amoeboid form	Mononte.
Merozoite		Spore; becomes later after entrance into erythrocyte amebula (s. myxopod).	Nomospore		Theilungskörper.	1898: amebula ... 1899: sporozoite.	Sporozoito (monogonico).
Macrogamete		Macrogamete (female gametocyte); young form: amebula s. myxopod).	Gynospore	Ovum	Female parasite	Macrogamete s. ooid.	Makrospora
Microgametocyte	Flagellated body.	Male gametocyte (young form: amebula s. myxopod).			Male parasite ..	1899: mikrogametogen.	Anteridio } gameti.
Microgamete	Flagellum ..	Microgamete	Androspore	Sperm	Spermatozoon ..	Mikrogamete s. spermoid.	Microspora
Ookinete (copula sporont).	Vermicula ..	Zygote	Gametospore	Oosperm	Würmchen	1899: zygote	Vermicolo } amfiente.
Oocyst (copula sporont).	Coccidium ..	Zygote	Gametospore ..	Oosperm	Coccidienartige Kugel.	1899: zygote	
Sporoblast		1899: zygotomere. 1900: mere, becomes blastophore.					Masse citoplasmatiche più o meno poligonale.
Sporozoite	Germinal rod.	1899: zygotoblast. 1900: blast.	Gametoblast s. gametoclast s. filiform young	Zooid	Sichelkeim	1899: spore	Sporozoito (amfignico).
Sporogony					Exogenous development.	Exogenous development.	Amfignonia (generazione sessuale) per sporogonia conitomica.

The extensive consideration which the subject has received in previous articles in the REFERENCE HANDBOOK (compare *Malaria, Mosquito in Relation to Human Pathology, Plasmodium Malariae*) renders it necessary here to insert only a brief diagnosis of the three species, and refer to the articles noted for further details.

Plasmodium malariae (Laveran 1883).—(Syn.: *Oscillaria malariae* Laveran 1883; *Plasmodium* var. *quartana* Golgi 1890; *Hæmameba malariae* Grassi et Feletti 1892; *H. Laverani* var. *quartana* Labbé 1894; *Pl. malariae quartanum* Labbe 1899.)

stops before the maximum of 30° C. is reached. *Plasmodium malariae* is found farther north than either of the other human malarial parasites, but does not extend into the tropics.

Plasmodium vivax (Grassi et Feletti).—(Syn.: *Hæmameba vivax* Gr. et Fel. 1892; *Pl. var. tertiana* Golgi 1889; *H. Laverani* var. *tertiana* Labbé 1894; *Pl. malariae tertianum* Labbé 1899.)

Young stages in the erythrocytes are very active. Pigment granules are fine, and light brown in color. The fully grown schizont completely fills the red cor-

puscle, which is usually swollen and bleached in color. This stage measures 0.008–0.01 mm. in diameter, and produces fifteen to twenty merozoites in schizogony, which requires for its completion just forty-eight hours,

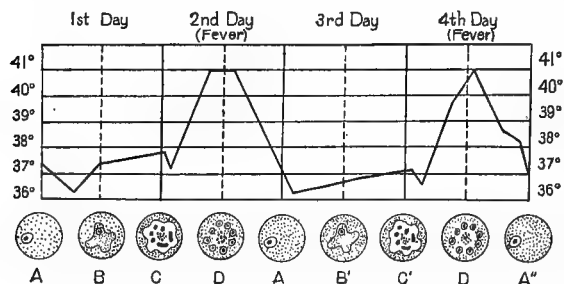


FIG. 5216.—Development of *Plasmodium vivax* in Relation to Temperature Curve of Patient. (After Doflein.)

whence the common names of tertian fever and tertian parasite. The pigment forms a solid mass in the centre, and the merozoites form a double ring about it, or more frequently an irregular mass. Schizogony occurs pre-eminently in the spleen. The gametes are abundant at a certain period, of spherical form, and distinguished from the schizonts above all in the form of the pigment, which is in coarse granules or bacilliform masses. They reach two to three times the diameter of an erythrocyte. The sporogony in the body of *Anopheles* requires eight days at a temperature of 28°–30° C.; 17° C. is the minimum for this stage of development. This corresponds to the occurrence of the disease in the tropics and subtropics. The relation of the body temperature of the host to the development of the parasite is well shown in the accompanying diagram (Fig. 5216).

Plasmodium falciparum Welch.—(Syn.: *Laverania malariae* Grassi et Feletti 1890; *Haemaphysa malariae praecox* Gr. et Fel. 1892, nec. *H. praecox* Gr. et Fel. 1890; *Plasmodium praecox* Doflein 1901).

This is the smallest of all human malarial organisms. Fully grown schizonts measure only 0.005 mm. in diameter. Young form very active; pigment moderate in amount, very fine in peripheral zone. The schizont may also remain unpigmented, and this form has been regarded as a separate variety. Multiple infection of an erythrocyte is not rare, and the assumption of a signet-ring form is very common. The erythrocyte shrinks during the growth of the parasite. In schizogony seven, ten, or twelve merozoites are formed, rarely twelve to fifteen, and these are small, being only 0.001–0.0015 mm.

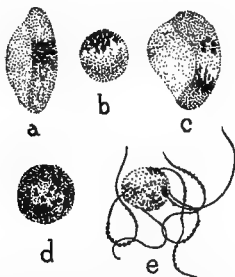


FIG. 5217.—*Plasmodium falciparum*; Development in stomach of *Anopheles claviger*. a, Macrogamete with remnant of erythrocyte; b, same one-half hour after ingestion by mosquito; c, microgametocyte with remnant of erythrocyte; d, same one-half hour after ingestion, the nucleus has divided several times; e, microgametes still attached to residual mass (so-called polymitus stage). Highly magnified. (From Braun, after Grassi.)

in diameter. The length of the schizogonic cycle is not well determined, as the process takes place in internal organs, especially the spleen. It is apparently irregular, though forty-eight hours seems most probable. The

gametes are crescentic or reniform, and originate especially in bone marrow. Further changes have been most carefully followed in this species. In the stomach of *Anopheles* these crescents become spherical (Fig. 5217) and the microgametes are formed and set free. The fertilization is completed by the fusion of a single microgamete with a macrogamete; and the resulting motile ookinet (Fig. 5218, a) penetrates the wall, entering first

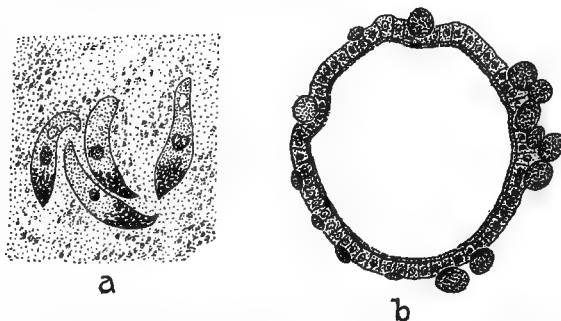


FIG. 5218.—*Plasmodium falciparum*. a, Ookinet in stomach of *Anopheles falciparum* thirty-two hours after ingestion; b, transsection of stomach with partly developed oocysts several days later. Magnified. (From Braun, after Grassi.)

an epithelial cell and coming later to lie between the layers of the wall (Fig. 5218, b). The oocyst forms no special covering, but increases rapidly in size. Sporoblasts and then sporozoites are formed; the latter have a length of 0.014 mm. and a thickness of 0.001 mm., and are produced to the number of ten thousand in a single oocyst. After the rupture of the latter they accumulate in the salivary gland, lying in the secretion either within the cells or in the duct itself, whence they are expressed in the act of biting (Fig. 5219).

The sporogony requires eight days at a temperature of 28°–30° C. and 18° C. is the minimum temperature for the infection of *Anopheles*. This species gives rise to the malarial fever designated as æstivo-autumnal, pernicioso, tropica, etc., and is epidemic only in the tropics and subtropics. This is the form which has been rated as a representative of another genus, *Laverania malariae*, by many observers. While its separation from the genus *Plasmodium* is perhaps a convenience, it seems hardly justifiable on scientific grounds, as the differences between it and the other species are not of generic rank.

Uncertain Species.—According to the work of certain investigators, particularly Celli, there exists a true quotidian malarial parasite, which is related to *Plasmodium*



FIG. 5219.—Section Through Dorsal Sac of Salivary Gland from *Anopheles* with Groups of Sporozoites of *Plasmodium falciparum* both in gland cells and in duct. Isolated sporozoite at right more highly magnified. (From Lang, after Grassi.)

falciparum, although smaller and completing the schizogony in twenty-four hours. The supposed species is found in Italy particularly in summer and fall, and is

regarded by most authors as at most a variety of *Pl. falciparum*. Still other forms from tropical regions have been regarded as distinct species without sufficient evidence as yet for this opinion.

Among American investigators Craig has especially emphasized the distinct character of the quotidian variety which, if his contentions are established, should certainly be considered a distinct species.

There are yet other hæmatozoa of which it may be said that their exact relationship has not been sufficiently demonstrated to give them a definite place in the system, but which in all probability will be included in this sub-order, though evidently not in the same genus with the malarial organisms just described.

In this connection should be noted the parasite of the spotted fever or tick fever of the Rocky Mountains, a new disease especially virulent in the valley of the Bitter Root River in Montana, where it has been known for twenty years, but present apparently also, though in milder form, in other parts of Montana, Idaho, Wyoming, Nevada, and Eastern Oregon.

In 1902 Wilson and Chowning described ovoid intracorpuseular bodies in stained blood smears and thought they demonstrated amœboid movements of such structures in fresh blood. These bodies they regarded as hæmatozoa and named *Piroplasma hominis*. Some later observations seemed to confirm their findings, but more extensive studies by several observers, especially Stiles and Ricketts, entirely failed to demonstrate the real existence of the supposed organisms which were in part apparently blood platelets and furthermore manifested such wide variations as to indicate their multiple origin. The similar organisms, said to have been found in the gopher (*Citellus columbianus*) and after experimental injection recovered from rabbits' blood, have also failed of confirmation, while Stiles has shown the marked variation from known types of piroplasmosis manifested by this disease.

On the other hand, Ricketts who had searched long and vainly for the organism was successful in 1906 in demonstrating that the disease may be transmitted to guinea-pigs and monkeys by injection of blood from spotted-fever patients and that it may then be maintained in the laboratory. Later the indigenous gopher was shown to be susceptible to inoculation with the disease. Ricketts also demonstrated positively that both male and female wood ticks (*Dermacentor occidentalis*) could transmit the disease by their bites, and followed out their life cycle in the laboratory. Whether they are mere mechanical vectors or act as true intermediate hosts is as yet undetermined, but the evidence obtained indicates that under some circumstances at least there is hereditary transmission of the disease to a second generation of ticks. Finally Ricketts showed that infected ticks exist under natural conditions in the Bitter Root Valley and that the virus is found in both the gut and the salivary glands of the infected tick. These facts indicate an animal organism rather than a plant germ, and a plasmic infection rather than one confined to blood cells. Further than this present evidence will not permit one to go safely.

Despite many reports the organism of yellow fever has probably not been discovered. It is apparently a hæmatozoon and is present in superficial blood only during the first three to five days of the disease. It is capable of passing through the pores of a filter and is not transmitted by fomites. The mosquito *Stegomyia calopus* is alone capable of transmitting the organisms, but only after an interval of ten to fourteen days after biting. These facts accord with a sporozoon whose life history includes the mosquito as an intermediate host and a sporogonic cycle having a length of ten to fourteen days. The organism has also been conjectured to be a spirochæte, some of which pass easily through the pores of a filter; and one observer has discovered in the kidney an organism of this type which was confined to the cells and lumina of the tubules. Thus far among none of the spirochætes has a cycle in an insect host similar

to that of the yellow-fever organism in the mosquito been definitely established.

Cyclasterion scarlatinale Mallory 1905.—(Syn.: *Cyclaster scarlatinalis* Mallory 1904, non Cott 1856). Schizogonic cycle only known. In and between cells of epidermis and in subadjacent lymph spaces. Schizonts round, oval, or slightly elongated, amœboid (?), 2 to 7 μ in diameter. Protoplasm finely reticulate, becoming coarser with growth when they reach 10 to 12 μ in diameter. Rosette bodies always spherical, 4 to 6 μ in diameter, with ten to eighteen segments also occur. Fully developed rosettes show evidence of merozoites separating and moving away. The coarsely reticular bodies may be stages in sporogony (?).

Superficially these bodies manifest a close resemblance to the *Plasmodium malariae* but appear one-third larger. The original discovery of Mallory has been confirmed by some observers and questioned by others. The latter regard these forms as degeneration products and some even claim to have found them where scarlet fever was positively excluded. Duval was able to collect them in large numbers from vesicles experimentally produced in the groin by rapid vesication. Here they were almost free from cellular elements of the body. This experiment and the morphology of the organisms, especially since it has been confirmed, leave little doubt of their independent nature. Their relation to scarlet fever still remains *sub judice*, though probable. Furthermore, their zoological position at this point is largely a matter of convenience. They have also been interpreted as species of *Cytoryctes* (q.v.).

Hæmatozoa have been described by various authors as characteristic of beri-beri or kakké, an endemic form of polyneuritis particularly prevalent in Japan and the Dutch East Indies. The infectious nature of this disease seems to be generally accepted, and at different times various forms of possible pathogenic significance have been reported from the blood. The most recent of these are amœboid bodies resembling malarial parasites, which have been studied and described at length by Glogner, and especially Fajardo. The latter demonstrates their presence in the blood in peripheral as well as inner organs, and their production of pigment and formation of spores of some sort; and yet the possible confusion with malarial or other hæmatozoa and the lack of proof concerning the distinct etiological relation to beri-beri have prevented any general acceptance of the rôle assigned to the organism.

In leukaemia also Löwit claims to have discovered amœboid organisms in the leucocytes, and to have followed their development even to sporulation, i.e., schizogony. (For further details see *Leukæmia*.) The parasitic nature of such structures cannot be regarded as established until they have been studied in life and not merely in preparations of fixed blood.

In dengue, an infectious disease epidemic in hot climates, and treated at length in an earlier volume (q.v.), good evidence has recently been furnished that the cause is a protozoon analogous to the malarial organism, and like it transmitted by the mosquito. It is an unpigmented pyriform body found in the erythrocytes though not abundantly, and is present in second and third attacks as well as in the first. The development is slow, requiring four to eight or even ten days, and in general appearance the organism suggests *Piroplasma bigeminum* of Texas fever in cattle or the organism of spotted or tick fever in man noted above. The discoverer, Graham, also found spores in the walls of the stomach and salivary glands of the mosquito, though this portion of the life history has not yet been clearly described; in one case the time required for it was, however, only forty-eight hours. In this case it is *Culex fatigans* which harbors the organism and transmits it, although other species may also be responsible. Graham has recently reported inoculation experiments, the results of which leave little doubt as to the cause of the disease and the method of transmission. The studies of Eberle, working on an epidemic of dengue in the Philippines, confirm in

part the schizogonic cycle. He finds the cycle requires only twenty hours and six to ten schizonts are produced. During the continuance of high temperature the organisms are abundant in the blood.

A long series of contributions concerns objects of supposed protozoan character which have been brought into

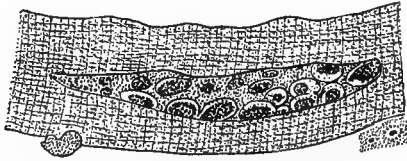


FIG. 5220.—*Sarcocystis tenella*. Longitudinal section of young stage with newly formed uninuclear pansporoblasts. Magnified. (From Wasielewski after Bertram.)

etiological connection with various pathological conditions of the most diverse type by investigators. Such are the pseudococcidia of epitheliomata, of sarcomata, of moluscum contagiosum, etc. Three views obtain as to the nature of these bodies, according to which they are blastomycetes or myxomycetes, sporozoa or other protozoa, and finally degenerative cell products. It cannot be said that their animal nature has been at all clearly demonstrated, and beyond the mere mention they have no right to consideration in this article.

In the subclass Neosporidia are included forms which in the adult condition are multinuclear, and which produce spores during the entire vegetative period. Spore formation is very characteristic. The organism forms a number of pansporoblasts, which divide again to form sporoblasts. The latter acquire a membrane and transform themselves with somewhat complicated changes into sporocysts, each of which develops within itself only a single sporozoite. Of the orders both the Sarcospor-

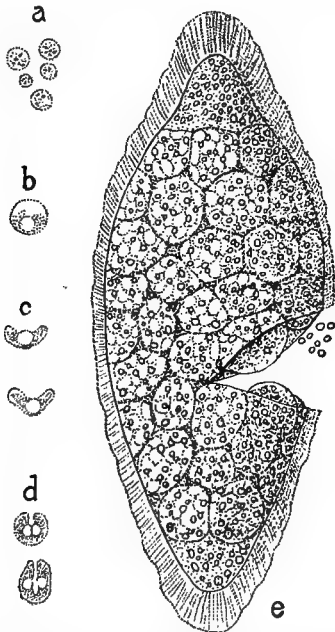


FIG. 5221.—*Sarcocystis miescheriana*. a-d, Development of sporozoites from sporoblasts; e, Full-grown sac, dissected out from muscle fibre, the radially striated capsule torn on the right to show the pansporoblasts within. Magnified. (From Wasielewski, after Manz.)

ridia and the Microsporidia are of importance here; they are but imperfectly known.

The Sarcosporidia possess an oval, elongate, or sacculate body (Fig. 5220), in which pansporoblasts are formed at a very early period. They parasitize at first intra-

cellularly the muscle fibres, but by the degeneration of these come to lie in connective tissue and develop to oval or spherical bodies of considerable size. In the youngest stages yet found uninuclear spheres 0.004–0.005 mm. in diameter with relatively large nuclei (0.002–0.003 mm.) occur in the endoplasm. The protoplasm forms a frame-work between these young pansporoblasts, which increase in size with age and become also multinuclear. While at the ends of the sacculate body new pansporoblasts are continually being formed, in the older ones nearer the centre the contents divide into many finely granular pale spheres, the sporoblasts.

In each of the latter is formed a single sporozoite which gradually assumes the definite form (Fig. 5221, a-d). These sporozoites are usually reniform, sickle-

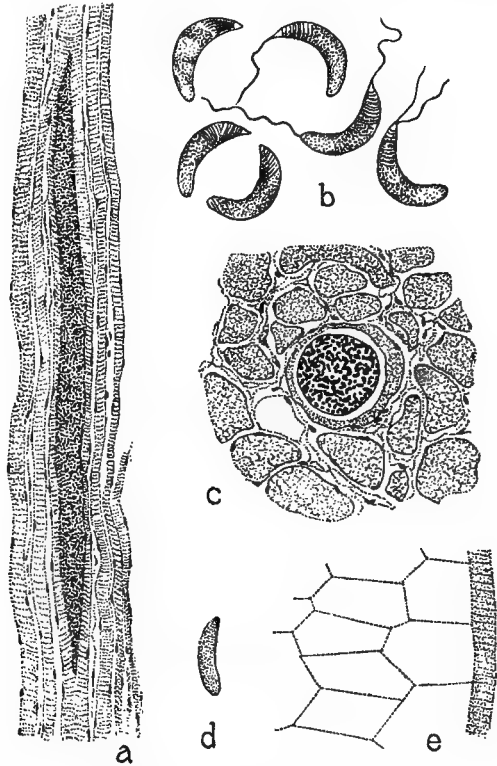


FIG. 5222.—*Sarcocystis Lindemanni* from Human Larynx (except b). a, Longitudinal section of muscle fibre with fully developed sac. $\times 250$. b, Transverse section of same. $\times 250$. c, Section showing chambers emptied of pansporoblasts. $\times 565$. d, Sporozoite. $\times 1,350$. e, Sporozoites of *S. Blanchardi* with polar filaments. $\times 875$. (b, From Wasielewski, after van Eecke; other figures from Doflein, after Barbaran and St. Remy.)

shaped, or crescentic and very small. Some investigators claim to have discovered a polar capsule, and this has been partly confirmed by some later observers. Polar filaments are present in some cases (Fig. 5222, b). Theobald Smith has observed the movements of the sporozoites, and finds that in *Sarcocystis muris* there is a peculiar gliding with sudden revolutions on the long axis. This is carried out without the assistance of flagella. Smith's experiments, which were very painstaking and extended over three years, demonstrate for this species direct infection by feeding muscle tissue in which was present the parasite with ripe, mobile sporozoites. Sarcosporidia are parasitic in vertebrata, chiefly mammalia, and are common in many domestic animals.

Miescher in 1843 found these parasites first as cylindrical sacs in the voluntary muscles of the house mouse. Some years later Rainey found similar structures in the muscles of the pig, and the common names of these structures, often visible to the naked eye, are associated

with these two investigators. The group has been but little studied, and the system is so imperfectly developed that it is advisable to omit all further mention of it, and to pass at once to a consideration of the one species which has been certainly obtained from the human body.

Sarcocystis Lindemanni (Rivolta 1878).—(Syn.: *Gregarina Lindemanni* Rivolta 1878; *Sarcocystis hominis* Rosenberg 1892; *S. Lindemanni* Labbé 1899.)

Protoplasmic body from the muscle fibres of the vocal cords, from 0.15 to 1.6 mm. long and from 0.077 to 0.17 mm. thick; membrane delicate, somewhat thickened at the ends (Fig. 5222, a), body distinctly chambered (Fig. 5222, e). Sporozoites (d) banana shaped, exceedingly numerous, 0.008–0.009 mm. in length.

The most certain case is that of Baraban and St. Remy, who found this form in the body of a criminal executed at Nancy. All the specimens of the parasite were in the same stage of development. The infected muscle fibres were swollen to fourfold their normal thickness. Several other uncertain cases are on record. As Theobald Smith remarks, the muscular system is not subject to the scrutiny which the viscera undergo in pathological investigations, so that the presence of these forms may be much more frequent and important than appears as yet. In the case of *S. muris* Smith has shown that the feeding of muscle tissue containing ripe mobile sporozoites to gray and white mice is followed by an invasion of the muscle fibres by the parasites, which readily become recognizable after the forty-fifth day. Nothing is known regarding the development of *S. Lindemanni*.

Among the Neosporidia and included in the order of Microsporidia are forms as yet poorly known which give rise to disease of great economic importance among lower animals. Chief of these is probably *Nosema bombyces* which produces the famous pébrine disease of silk worms. Here belong probably also the following human parasites:

Rhinosporidium kinealyi Minchin and Fantham 1905. —Youngest stage granular, protoplasmic, irregular, possibly amœboid, multinucleate masses in submucous connective tissue, measuring 1 to 1.5 μ in diameter. After formation of a cyst wall each gives rise to spherical pansporoblasts at first only 2 to 2.5 μ in diameter. These develop progressively from the centre toward the periphery of the mass at the expense of the peripheral zone of protoplasm. The developed pansporoblasts measure 5 to 6 μ and are surrounded by a cell wall which encloses minute spores, from four to fifteen in each spore-morula. The spores are minute spherical bodies each with a single nucleus. According to Beattie some show in addition a smaller, similarly stained granule, in general appearance much like that of the Leishman-Donovan body. By bursting of the cysts the spore morulae are scattered in the surrounding tissue. This endogenous reproduction explains the tendency to recurrence manifested by the tumors which the organism produces.

The parasite gives rise to small, pedunculated tumors in the nasal fossæ. The tissue is studded with minute white dots visible to the naked eye, which appear under the microscope as cysts filled with granular bodies in three zones as noted above. Many cases are on record from India, where the growth appears to be common among natives. A single case, recently reported by Wright, concerns a farmer who had never been away from the vicinity of Memphis, Tenn. The location of the growth near the vestibule of the nose suggests infection through the work of the finger nails.

The method of spore formation manifests affinities with the Neosporidia, and yet in the absence of knowledge concerning the life cycle and the peculiar nuclear conditions more precise relationship cannot be determined. Until its definite relationship becomes clearer the organism may tentatively be placed among the Microsporidia, in spite of some radical differences between it and members of that group.

The class Infusoria holds the highest rank among Protozoa, and its members are at once distinguished by the presence of peculiar organs of locomotion in the form of

fine hair-like protoplasmic processes, the cilia, which are present in at least some part of the life history of all individuals in the group. By virtue of the greatly inferior length, the much larger number present on each animal, and the simple synchronous movement cilia are easily distinguished from flagella. The external zone or ectoplasm is more highly differentiated than in the forms of Protozoa thus far considered, and the body has in consequence a more permanent form, which tends to acquire in all free species a bilaterally symmetrical structure. In the ectoplasm one finds special contractile fibrils, or myophanes, and peculiar unexplained bodies known as trichocysts. The cilia are arranged in rows, and occasionally fuse into vibrating membranes or stylet-shaped masses, cirri, in furtherance of the motor function. The firm ectoplasm forms at the mouth opening (cytostome) a groove (peristome), or a peculiar funnel-shaped pit (cytopharynx), which serves to admit food particles to the interior of the body. A differentiated anal orifice (cytopyge) is only rarely found. The contractile vacuole is always present, and often two or more occur with a more or less extended canal system branching in all directions.

One of the most striking peculiarities is found in the nuclear conditions. Typically two nuclei are present; a large somatic nucleus or macronucleus, and a small sexual nucleus or micronucleus, which usually lies close to the former. The macronucleus is always single, but there may be several micronuclei to each cell. The ordinary process of reproduction is fission or gemmation, and in this the macronucleus divides amitotically while the micronucleus undergoes indirect or mitotic division. At times one finds conjugation, or temporary and partial fusion of two individuals with the destruction of the macronuclei and of a certain portion of each micronucleus, while the remainder of each micronucleus on each side is divided equally between the two individuals. From the portions of the micronuclei fused there arise new macronuclei and micronuclei. This process has generally been looked upon as one of rejuvenation, and necessary for the continued existence and reproductive power of the individual. Certain recent investigations leave this somewhat uncertain. The complicated details of the process find, however, an evident parallel in changes connected with the fertilization of higher forms, or the union of egg and sperm cells.

Encystment is frequent, and the evident means of providing for unfavorable changes in environment, such as drought, temperature changes, etc. In parasitic forms it is related to the necessary interval of transport to a new host. In the majority of cases these protozoa are commensals rather than true parasites, and in some instances are even said to be of mutual advantage to the host, and consequently symbiotic in character. The two subclasses are distinguished on the basis of the permanence of the ciliary covering, which is constantly present in the Ciliata, save during encystment, but which is found only in the young forms of the Suctorio. The latter are also supplied with peculiar sucking tubes for taking in nourishment. They do not furnish any forms found in the human body.

The Ciliata are present in large numbers in all freshwater bodies, and manifest great variety of structure. They furnish many ectoparasitic species on water-living vertebrates and a few endoparasitic in higher forms, including man. The various orders into which the Ciliata are divided are based upon the number and arrangement of the cilia in the adult form. Only two of these orders call for attention here. In the Holotricha there is no spiral zone of prominent cilia or membranelle leading to the cytostome, and the body possesses only small cilia which are more or less generally distributed. The Heterotricha have an adoral spiral zone of larger cilia, but the remainder of the body is uniformly finely ciliated.

Of the Holotricha one species has been reported from man. It belongs to the genus *Chilodon*, the distinctive features of which are included in the description of the species which follows.

Chilodon dentatus (Dujardin 1841).—(Syn.: *Loxodes dentatus* Duj. 1841; *Ch. dentatus* Guiart 1903.)

Oval, 35–55 μ long by 25–35 μ broad, flattened in ventral face, dorsal aspect strongly arched. Anteriorly a flexible membranaceous projection curved toward the left and carrying several rows of cilia on the lower aspect. Granular endoplasm confined to posterior inflated region; ectoplasm in a thin peripheral layer and forming the anterior projection. Mouth ventral, in anterior portion of the endoplasmic region, normally contracted and hardly visible, cytopharynx directed dorsally and recurved ventrad so as to form almost a complete circle. Two contractile vacuoles, macronucleus large, spherical, in posterior region.

This infusorian has been found once by Guiart, as a parasite of the human intestine in Paris, France. The animals were present in large numbers in the mucus from dysenteric stools. Care was taken to control the source of the parasite and to avoid contamination from external sources, with the result of obtaining from the dejecta on the second day after passage pure cultures of the infusorian. It is a common free-living species, and must be classed in this instance merely as an accidental parasite. Close examination of faecal discharges will undoubtedly show the occasional occurrence of many such, especially when the resting spores happen to be abundant in the local supply of drinking-water. In this case there is nothing to show that the resting spores did not simply make the passage of the canal, and then develop almost at once in the discharges. The extreme sensitiveness of the species to changes in the environment, which has been commented upon by Guiart himself, makes this explanation of the case more probable. One should recall in this connection the record of Schaudinn, that the resting spores of a Rhizopod, *Chlamydomorphys stercorea*, must make the passage of the alimentary canal in man or other animals in order to undergo development. In this case, indeed, the resting spores open in the colon and an amœboid organism emerges which does not assume the testaceous form of the adult until after the faeces are discharged from the body.

The order of the Heterotricha, already generally characterized, includes three species under two genera, which have been reported from the human host. The first belongs to the genus *Nyctotherus* Leidy 1849, which contains flattened reniform species with a peristome along the concave side from the anterior pole to the cytostome at the centre. The cytopharynx is more or less arcuate. The macronucleus is large and nearly central in location. A single contractile vacuole is present. The species of

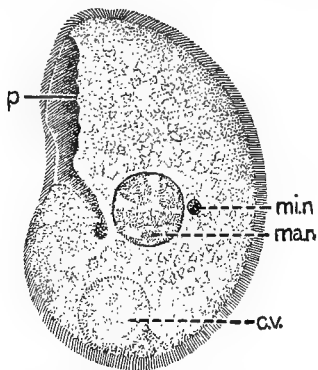


FIG. 5223.—*Nyctotherus faba*, Living. c.v., Contractile vacuole; ma.n., macronucleus; mi.n., micronucleus; p, peristome. Magnified. (After Schaudinn.)

this genus occur as parasites in the alimentary canal of Anura, Myriapoda, and Insecta. A single form has been found twice in the human alimentary canal.

Nyctotherus faba Schaudinn 1899.—Body reniform, somewhat flattened dorsoventrally, left side convex, right concave and notched in the centre. Anterior end

bent to the right a little, and on the right side slightly cut out; posterior end broadly rounded (Fig. 5223). Length 0.026–0.028 mm., breadth 0.016–0.018 mm., thickness 0.01–0.012 mm. Peristome a narrow longitudinal slit just at right margin of body, extending from near anterior end to middle of body. Cytopharynx tubular, short, and without guide spine at entrance. Cilia very fine and delicate as well as short. Ectoplasm thin, endoplasm granular, alveolar and without food vacuoles. Contractile vacuole large, located left of middle, near posterior end, emptying through the special anal tube. Macronucleus spherical, 0.006–0.007 mm. in diameter, with chromatin in four or five solid masses near periphery, leaving the intervals filled by a non-staining linin network. Micronucleus 0.001–0.0015 mm. in diameter, spherical or oval, ordinarily next the macronucleus. Fission and conjugation were not observed. Encysted form oval, easily recognized by the strange macronucleus.

This species has been found only once in Berlin in a patient suffering alternately from diarrhoea and constipation. It occurred in large numbers in the faeces taken direct from the intestine, and was accompanied by *Balantidium minutum* and eggs of *Anguillula* (?) and *Anchylostoma*. The species has an especial interest here, since the German physicians suggest from the history of the case that the infection may well have been attained in the United States, where the patient had lived for some time previously. A pathogenic rôle has not been attributed to the species.

Castellani has described as *Nyctotherus africanus* a ciliate found in 1905 in a Baganda negro. It was in form like a butter-ladle, 40 to 50 μ long by 25 to 40 μ wide, covered by fine cilia except at the basal margin where longer cilia are present. In arrangement of chromatin the macronucleus resembles that of *N. faba*. Neither oral groove nor food vacuoles were observed. Its peculiar form will not permit its inclusion in this genus. No pathological significance could be attributed to the parasite.

Stiles reports in recent correspondence that he has encountered several cases of ciliate infection which could not be identified and at the time more exact study was impracticable. The attention of physicians should be directed more carefully to this group of organisms.

Writers on tropical diseases recognize generally a type of protozoal dysentery which they attribute to "*Balantidium*." A recent contribution records a similar case from Utah. A more precise study of these organisms and of their life cycle is imperatively demanded, since data are lacking to show what species is concerned, if indeed the organism actually belongs to the genus named.

The genus *Balantidium* includes species of oval or ellipsoidal form, circular in transsection, with the anterior end somewhat tapering. The peristome has the form of a flattened funnel with the cytostome at its base. Two contractile vacuoles on the right side, sometimes two others on the left. Cytophyge terminal; macronucleus oval or reniform. The five known species are parasitic in the alimentary canal of man (two species), pig (one species), and amphibia, and in the body cavity of polychaetous annelids. For the distinction of the human parasites a key to all five species is necessary. That given here is taken from Schaudinn.

1. Peristome extends to equator of body or further, cytopharynx present 2
Peristome much shorter, cytopharynx wanting 3
2. Four contractile vacuoles, macronucleus reniform, cyst spherical. *B. entozoon* Clap. and Lachm.
One contractile vacuole, macronucleus spherical, cyst oval. *B. minutum* Schaudinn
3. Two contractile vacuoles. 4
One contractile vacuole, macronucleus oval, cyst spherical. *B. duodenii* Stein
4. Body elongated, spindle-shaped, or cylindrical,
B. elongatum Stein
Body oval. *B. coli* Stein

Balantidium coli (Malmsten 1857).—(Syn.: *Paramacium coli* Malmsten 1857; *B. coli* Stein 1867.)

Form oval, slightly truncated anteriorly with very short infundibuliform peristome which lies just to the right of the anterior tip and leads to a short cytopharynx (Fig. 5224). Body 0.07–0.1 mm. long by 0.05–0.07 mm. broad. Ectoplasm and endoplasm distinct; latter with

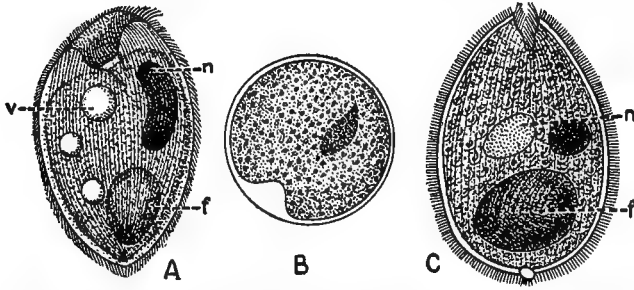


FIG. 5224.—*Balantidium coli*. A, C, Free; B, encysted; n, macronucleus; v, contractile vacuole; f, food mass. Magnified. (A, After Leuckart; B, C, from Braun, after Casagrandi and Barbagallo.)

drops of oil and mucus, and according to some observers red and white corpuscles from the host. Macronucleus bean-shaped or reniform, with the small spherical micronucleus adjacent to it. Two contractile vacuoles located on the right side, but no permanent cypotype. Fission of the free form has been observed. Conjugation has also been seen. Cysts are spherical and possessed of an impervious membrane.

This species inhabits the colon of man and the pig. In the latter it occurs also in the rectum and cæcum, and is present regularly in large numbers. The pig may be regarded as the normal host, and in it this species excites no abnormal symptoms. The encysted forms evacuated with feces are supposed to bring about the transfer of the species all the more easily that the pig is coprophagous; and yet experimental infection has been unsuccessful even in the pig. Grassi and Calandruccio have demonstrated that experimental infection of man is not successful in the case of healthy individuals. The occasional introduction of encysted forms may, however, bring about successful colonization of the canal whenever any pathological conditions exist in the colon, although Grassi and Calandruccio argue from the slight difference in size and the failure of their experiments that the forms found in man are not of the same species as those from the pig. These conclusions do not seem to have found even limited acceptance.

Malmsten discovered *Balantidium coli* in 1857 in a man who had recovered from an attack of cholera two years before, but had since suffered from diarrhoea. The parasites were abundant in the bloody discharge of a rectal abscess, and even after its disappearance persisted in the feces, from which they finally disappeared as a result of the use of acid enemata. In the necropsy of a subsequent case the exact seat of the parasite was determined as the anterior region of the large intestine.

Many cases have been reported from man since then. Shegalow lists sixty-three in all from Russia, Germany, Scandinavia, Finland, Italy, Cochin China, Sunda Islands, and the United States of America. Strong and Musgrave have added the Philippines to this list. Strong listed 117 cases, all before 1902, in which the mortality was thirty per cent., and since then the list has been greatly augmented. While this parasite has been observed regularly in obstinate diarrhoea, its disappearance is not accompanied with the cessation of the symptoms in all cases, and *Balantidia* have been found after the diarrhoea has stopped. The earlier idea that these protozoa were the exciting cause of the intestinal disturbances has accordingly given way in part to a view that these protozoa continue and extend the diseased condition, but are not sufficient to cause it. Some au-

thors report, however, that the species penetrates the intestinal wall and causes abscesses in the deeper layers. Solowjev claimed even to have demonstrated them in the blood and lymph vessels of the intestinal wall. This has recently been confirmed by Strong and Musgrave.

These authors, together with several other very recent contributors to this subject, contend very strongly in favor of the pathological rôle played by the parasite. In most post-mortem lesions have been found similar to those of amœbic dysentery. Brooks found in apes in New York extensive ulcerations in the cæcum, irregular in contour with undermined borders. The mucous and submucous coats were destroyed and the parasites were present in great numbers in the ulcerations, especially on the floor and along the sides. They even pass beyond the limits of the ulcers, apparently following the course of the lymphatics and blood-vessels. It was surmised that the parasites entered the submucosa from the crypts of Lieberkühn, in the depths of which they were often found. The *Balantidia* were found in the diarrhoeic stools, but disappeared with recovery of the host. But relapses were frequent, and each time the parasites reappeared in the feces.

This is explicable on the basis of their position deep in the glands of the intestinal wall, and emphasizes the difficulty of completely destroying them and preventing a recurrence of the disease.

It is difficult to avoid the conclusion that positive proof of the etiological significance of these forms is given by the presence of abundant parasites in the lesions and in the tissues in advance of the pathological changes, and also by their occurrence in the depths of glands and in the submucosa before the start of such lesions at these points. The opponents of this view regard the rôle of the protozoa as secondary, and look upon bacteria as primarily responsible for the lesions.

Whether *B. coli* is capable of producing a primary erosion of the intestine has not been conclusively demonstrated, though many believe that it has this power. However, if a lesion exists from any cause, the parasite is certainly capable of continuing the process and of modifying and producing in connection with accompanying bacteria fairly constant and characteristic pathological lesions. Since the publication of Strong's photographs one can no longer doubt that *Balantidia* do occur in the tissue and blood-vessels of the intestinal wall. All recent evidence supports the view that the parasite is pathogenic and its presence in stools in cases of intestinal disturbances has the same significance as the presence of amœbæ in dysentery.

This species is known to occur abundantly in some parts of this country as a parasite of the pig, and its more frequent presence in the human host than records hitherto made would show may easily be disclosed by more careful examination. It should be noted that many of the cases already on record come from the country where the chances of accidental infection are naturally greater. It is there accordingly that one should look for evidence of more extended infection of the human host. Lack of records in the past may well be due to lack of precise examination among the very cases in which the parasite is most likely to occur.

Balantidium minutum Schaudinn 1899.—(Syn.: *Colopoda cucullus* Schulz 1899.)

Body compressed pyriform or oval (Fig. 5225). Length 0.02–0.032 mm.; breadth 0.014–0.02 mm., or in the ratio 3:2. Anterior end bluntly pointed, often slightly twisted dextrad or sinistrad. Posterior end broadly rounded. Peristome a slender cleft, broader anteriorly, pointed posteriorly and deeper; extending from near anterior tip to centre of body; in the living animal continually opening and closing; left margin with hyaline membrane. Adoral cilia heavier and longer than those of the body generally, only on the left peristome margin beneath the membrane. Body cilia long (0.007–0.008 mm.) slender. Hyaline ectoplasm thin, distinct from

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granular endoplasm, which contains many vacuoles. These are filled with fine granules, and large food masses or excretory crystals are not present. Contractile vacuole single, near posterior end on left side. No permanent cytophyge. Macronucleus spherical, 0.006-0.007

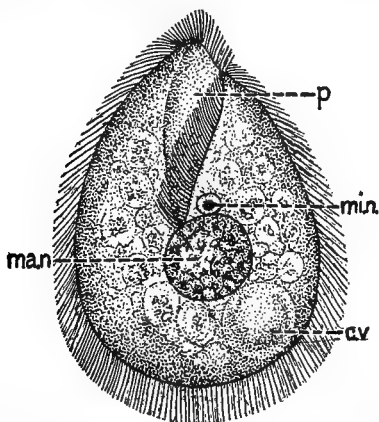


FIG. 5225.—*Balantidium minutum*. Living. Abbreviations as before. Magnified. (After Schaudinn.)

mm. in diameter; centrally located. Micronucleus single, anterior to macronucleus at its surface, 0.001 mm. in diameter. Division occurs, but conjugation has not been observed. Cyst oval.

Reported twice, once in company with *Nyctotherus faba* (q.v.) and once in Berlin also without that species. In both cases this form was abundant during the diarrhoea, but, with the exception of a few cysts, disappeared as soon as the stools became firmer. Purgatives brought the infusorians again in numbers into the stools. This condition indicates that they inhabit the small intestine, perhaps the duodenum, rather than the colon, and make their appearance when carried outward by more fluid contents and rapid passage through the canal. As other species of the genus are harmless commensals in the canal of Amphibia, this species is probably not pathogenic. It should be kept in mind that confusion of *B. coli* and *B. minutum* may occur if the examination is not made with precision, and perhaps some cases of the former, already on record, actually concern the latter species.

As pseudo-infusoria may be designated a long series of structures reported from various sources, and often the object of repeated discovery by those unfamiliar with the field. Thus in mucus or sputum in case of affection of the air passages, bodies moved by cilia have been interpreted as genuine parasites and assigned an etiological rôle in the disease. In contravention of this view may be urged the variable and irregular form of such bodies, their rapid and special degeneration and their source, which amply demonstrate their origin as detached ciliated cells from bronchi, trachea, or nasal cavity. Such bodies are the asthma parasites of Salisbury, and the protozoa of whooping-cough described by Deichler and Kurloff.

Much less worthy of serious attention are the reports of various writers, especially Lindner, that certain forms, well known as free-living species, namely, unstalked vorticellids, are the cause of various gastric disturbances in man and certain domestic animals. The statements of Schaudinn, that he has found repeatedly active vorticellids in fresh feces, but only after water enemas, is sufficient indication of the means by which such marvellous discoveries as those of Lindner and others are achieved. Quite recently I was asked to examine a slide containing organisms from fresh urine, and these were not echinococcus bladders as diagnosed, but unmistakably free-living forms, and probably contracted rotifers whose presence was due to the contamination of the vessel, or possibly of the sample of urine examined.

Henry B. Ward.

PYLORUS, STENOSIS OF.—The first description of this condition, though not under this title, appeared in an article published in New Haven by Dr. Hezekiah Beardsley in 1788. This paper was republished at the suggestion of Dr. William Osler in the *Archives of Pediatrics* for May, 1903. The description of this ancient case was accompanied by the necropsy findings. Martin in 1826 and Pauli in 1828 described cases. The next mention of the disease was by Williamson in 1841. But the subject was brought prominently before the medical profession through a paper read by Hirschsprung before the German Pediatric Society in 1887. Since then the condition has been observed quite frequently, and numerous papers dealing with various phases of the subject have appeared. The main discussion has turned upon whether the condition is one of congenital hypertrophy, whether it is one of acquired hypertrophy the result of spasm, or whether the stenosis is simply due to spasmodic contraction of a normal pylorus. From a consideration of the cases reported, together with the results of autopsy findings and of inspection during life at the time of surgical operations as well as the study of the sections removed at the time of the operation, it is definitely established that in some cases there is hypertrophy of the muscular coats of the pylorus and that in certain cases this hypertrophy is congenital. It is probably true that the hypertrophy increases after birth because of the spasm which exists to a greater or less degree in all cases. There are various degrees of this congenital and acquired hypertrophy. Moreover, there are many cases that give some or all of the symptoms of cases of true hypertrophy in which there is no thickening of the muscular coat and the symptoms are produced by spasm alone. These last cases may be considered as closely allied to cases of severe vomiting from spasmodic closure due to gastric indigestion.

Hypertrophic pyloric stenosis, according to Pfandler, occurs almost entirely in the Anglo-Saxon and Scandinavian races. From the Latin or Slavic countries few or no cases have been reported. Boys are more frequently affected than girls. More than one-half of the cases occur in breast-fed children and over one-third in those who have never had anything but breast milk up to the time of their sickness. The age of the child at the time when the attack comes on is from 1 to 4 days in one-fourth of the cases, 4 to 14 days in one-fourth of the cases, 2 to 3 weeks in one-fourth of the cases, and 3 to 8 weeks in the final quarter of the cases.

Pylorospasm.—Reports of pylorospasm in infants have come from the most diverse countries; so that this condition has a wide geographical distribution. There is perhaps also a family predisposition. Hereditary factors and especially a neuropathic taint seem to play a rôle in its production. The first signs of the disease appear on the average later than in the case of hypertrophic stenosis, not often, however, after the end of the

EXPLANATION OF
PLATE LXII.

EXPLANATION OF PLATE LXII.

FIGS. 1 and 2 show numerous large and small scarlet-fever bodies in and between the epithelial cells of the rete mucosum. In Fig. 1 is a large body in a lymph space of the corium just underneath the epidermis. Several of the bodies suggest fixation while in amœboid motion.

FIGS. 3, 5, and 6 are coarsely reticulated forms which may be degenerated forms of the scarlet-fever bodies, or stages in sporogony.

FIGS. 4, 8, and 9 probably represent stages preceding the radiate bodies. In Fig. 9 the bodies lie in a lymph space. It shows also four small forms which apparently have just freed themselves from a rosette.

FIGS. 7, 10, 11, 12, 13, 14, and 15 show different stages in the development of the radiate bodies.

FIG. 10 is the earliest stage; there is a distinct central body and a definite regular arrangement of granules at the periphery. **FIGS. 7, 11, and 12** show a little later stage of development; 11 and 12 are optical sections, while 7 is a surface view. Moreover, in Fig. 7 the body lies free in a lymph space in the corium. The segments begin to show a certain amount of lateral separation from each other.

FIG. 13 is a still later stage; the segments are increasing in size and are more or less free from each other, although most of them are still attached to the central body. In Fig. 14 the segments are all free and enlarging, although still grouped around the central body. In Fig. 15 three bodies are still grouped around the central body, which is free.



PROTOZOÖN - LIKE BODIES FOUND IN FOUR CASES OF SCARLET FEVER.

(AFTER F. B. MALLORY)

*Copied in monochrome tint from the colored drawing in the original paper
Journal of Medical Research, No. 4, Vol X, 1904.*

first year. It occurs especially in artificially fed children suffering from some alimentary disturbance.

SYMPTOMS.—The infant who is healthy at birth, so far as appearances go, begins when two or three weeks old to vomit the nursings. At first the vomiting is not much more than frequently occurs from overloading the stomach, but it is persistent and increases. Sometimes the infant will not vomit for several feedings and then will eject forcibly a quantity of partly digested milk sufficient to represent several nursings. The vomitus is projected with such force that it may pass in a jet or stream to a distance of three or four feet, or "across the bed," as the mothers often report. The vomiting occurs without evident signs of indigestion, although the vomitus represents various stages of gastric digestion. If dietetic and medical measures fail to relieve the condition, the symptoms persist and increase. There is constipation, the stools being very small, and at later stages consist simply of brownish or greenish mucus like the meconium stools of the newborn baby. Meantime the baby loses weight, becomes emaciated, and finally presents the picture of marasmus.

Examination of the abdomen reveals peristaltic waves passing across the epigastrium, usually from left to right. These are more apt to occur shortly after food has been taken. The appearance has been well compared to that of a small ball rolling across under the abdominal wall. At times the waves are doubled, and occasionally their direction is reversed. Palpation in cases where the liver is not enlarged reveals a hard mass at the pyloric end of the stomach, feeling much like a spool or an olive under the abdominal wall. The peristaltic waves of the stomach can also be felt. Percussion reveals frequently enlargement of the stomach, its lower border extending a variable distance toward the umbilicus. The symptoms in detail are as follows:

(A) **HYPERTROPHIC STENOSIS.**—(1) *Vomiting* occurs at first only now and then, later more often, and finally after almost every feeding. The vomiting takes place either at once or from one to three hours after the nursing. The vomited material contains mucus, together with the partially digested food, and has a strong odor of butyric acid; it is seldom foul. There is, according to most observers, never any bile present, although exceptions to this rule have been reported by Schwyzer and by Saunders. The vomiting is not accompanied by any signs of nausea or collapse.

(2) *Visible peristalsis* is a characteristic symptom and one which is seldom absent. This is not accompanied by any pain. If the abdomen is in a good light, there can be seen travelling across the epigastrium from left to right successive waves; these generally stop at the median line, then begin again. At times they are multiple; and occasionally they pass from right to left. The significance of this symptom is less than formerly supposed, since cases of pyloric spasm show it, and it is also present in emaciated or rachitic infants that have gastric dilatation with vomiting. Again, according to Rotch, visible peristalsis may not be observed in true cases of hypertrophy.

(3) *Palpable Tumor of the Pylorus.*—This is an inconstant symptom, but very valuable when present. It appears about the end of the fourth week of the illness. Slightly to the right of the median line, often through the space between the rectus muscles, there can frequently be felt a resistant tumor about the size of a hazelnut, an olive, or a spool. It was once thought that a palpable pylorus was absolutely diagnostic of hypertrophy, and that when present it demanded surgical intervention. It is now known, however, that cases can recover under medical treatment even when palpable pylorus is present. Neild reported two cases in which the pylorus was both visible and palpable that recovered after treatment by small doses of opium; Stamm reports two cases in which there was a palpable tumor together with persistent vomiting, both cases recovering under dietetic treatment, and recently a case was re-

ported by Herrman in which the pyloric tumor and peristaltic waves were present, but which recovered under the use of warm compresses after operation had been advised but not permitted. On the other hand, without the presence of pyloric tumor it is unsafe to make a diagnosis of hypertrophic stenosis of the pylorus, since visible peristalsis and the other symptoms are frequently present in cases of gastric or pyloric spasm without stenosis.

(4) *Loss in Weight.*—This depends upon the loss of water and fat. The infant may lose an ounce or more daily and finally present the picture of marasmus, with subnormal temperature, sunken fontanel, and anæmic redundant skin hanging in folds over the extremities. Heubner saw, in two cases of pylorospasm, weights of 2.6 kg. in a six-months' child, and of 2.5 kg. in a four-months' child.

(5) *Obstinate Constipation.*—The stools are very small, or there may be none at all for from three to twelve days; then the stool is like that of starvation, and looks like meconium.

(6) *Scanty urine* depends directly on the amount of water absorbed. The urine passed is, of course, rich in solids.

Symptoms (4), (5), and (6) are a direct result of the vomiting.

(7) *Sunken abdomen and dilatation of the stomach* are symptoms of less importance.

(8) *Motor Insufficiency.*—If the stomach tube is used three or four hours after a feeding, there is withdrawn a large quantity of partially digested food, with usually more than the normal amount of mucus. At times, too, a mucous plug is obtained by lavage.

(9) *Hyperacidity* has been found in certain cases, as has also hyperchlorhydria. This finding is in contrast to the usual low acidity of most other digestive disturbances in infancy.

(B) **PYLOROSPASM.**—The early symptoms are similar to those of hypertrophy, but less severe. The vomiting is not so frequent nor so regular; the intervals between the spells being longer; moreover it is not so explosive, being more in the nature of regurgitation. The stools are often green, containing mucus, and the constipation alternates with diarrhoea. In severe attacks wasting follows as a result of the digestive disturbances and the vomiting. Visible peristalsis of the stomach and occasionally also palpable tumor of the pylorus are present. Hyperacidity and hyperchlorhydria are both found at times. Infrequently a spasm of the pylorus is met with as a manifestation of some general nervous disorder, just as are also nystagmus and the signs of tetany.

COURSE.—Unless food is able to pass the pylorus in sufficient quantity, the patient naturally starves to death notwithstanding attempts at rectal feeding, because this is insufficient to maintain life for any length of time, although it may aid temporarily. Signs of improvement are as follows: There is a cessation of the vomiting and a reappearance of milk stools; the loss of weight ceases and the fretful whining disappears; finally the peristalsis becomes less evident and gradually disappears entirely.

PATHOLOGY.—Cases that have come to autopsy have revealed one of three conditions: First, a normal stomach; second, contracted pylorus without hypertrophy; third, a contracted and hypertrophied pylorus. It is of these last cases that most careful study has been made, and these are the ones that support the contention of a congenital hypertrophy. In nearly all the reported cases there is hypertrophy of the circular muscular coat of the pylorus. In most of them there is also hyperplasia of the submucosa, and in a few there is thickening of the mucous membrane. In Dornier's fatal case (not operated on), the anatomical diagnosis was "stenosis of the pylorus from fibrous thickening of the submucosa and hyperplasia of the circular muscular coat." According to Heubner the muscular hypertrophy affects the musculature of the whole stomach, but the pyloric region to a greater degree.

PATHOGENESIS.—There are many theories in regard to this condition. It is claimed by some (Cautley and Peden) that in her effort to supply an efficient pylorus Nature exceeded the needs of the case and deposited an excessive amount of muscular tissue in that region. Thomson thinks that there is hypertrophy due to excessive functioning depending upon nervous inco-ordination. He calls the condition congenital gastric spasm, and thinks that it is analogous to the spasm of the pylorus that occurs in Reichmann's disease in adults. Cunningham from his anatomical investigations on lower animals, and Neild from his clinical experience with adults, believe that the stenosis is due to spasm. Wernstedt thinks that the cases in which there is hypertrophy are really congenital, agreeing with Cautley as to their pathogenesis. But in regard to the other cases of stenosis, he thinks they are due to spasm. The accompanying table, taken from Pfaundler, gives succinctly the various theories as to the origin of the condition:

boys are somewhat more liable to the affection than girls. Heredity seems to play a rôle, Rolleston having met three cases in the same family, and Henschel and Heubner having had the same experience. Rolleston thinks that this family peculiarity is comparable to that met in congenital obliteration of the bile ducts. As regards pylorospasm, one would expect that a nervous heredity would be a predisposing cause. Undoubtedly gastric indigestion, which is more apt to occur in artificially fed infants, is at times the causative factor in pylorospasm. In both conditions, however, there must be some underlying peculiarity either of the nervous mechanism or in the musculature at the pyloric end of the stomach. As a matter of fact, the etiology of the pyloric stenosis is still in obscurity.

DIAGNOSIS.—The important signs for diagnosis of pyloric stenosis are: (1) projectile vomiting without evidences of indigestion; (2) visible peristalsis; (3) palpable pylorus. In addition to these symptoms, obstinate constipation and the finding of food remains in the dilated

SYNOPSIS OF THE MOST IMPORTANT THEORIES CONCERNING THE NATURE AND ORIGIN OF THE HYPERTROPHY IN PYLORIC STENOSIS.

(From Pfaundler in Pfaundler and Schlossmann's "*Handbuch der Kinderheilkunde*.")

- | | | | | |
|--|--|--|---|--|
| <p>I. The hypertrophy is only apparent—(produced by persistent post-mortem contraction—no increase in thickness, no true stenosis.</p> | <p>A. Stomach at necropsy absolutely normal; during life also, function is perfect.</p> <p>B. Stomach at necropsy hardened in systole, for the same reason that during life there is an abnormal tendency to spasm of the pylorus.</p> | | | |
| <p>II. The hypertrophy is real (increase in mass); it is congenital and primary, producing the stenosis (and perhaps secondary spasms).</p> | <p>A. Simple excess of development; local overgrowth (Cautley, Peden: "Nature, in her anxiety to provide for an efficient closure of the pylorus, surpasses her aim").</p> <p>B. True tumor, such as leiomyoma or fibromyoma (Löbker and other surgeons).</p> <p>C. Atavism; phylogenetic retrogression (to conditions found in certain edentates; Flynn, Murray).</p> <p>D. Ontogenetic retrogression (to condition present in early foetal life; Ibrahim).</p> | | | |
| <p>III. The hypertrophy is real but secondary (acquired in foetal or in extra-uterine life.</p> | <table border="0"> <tr> <td style="vertical-align: top;"> <p>A. An exercise hypertrophy, the result of primary spasm (Thomson).</p> <p>B. A compensatory hypertrophy following stenosis:</p> <p style="margin-left: 20px;">a. as a result of primary spastic stenosis;</p> <p style="margin-left: 20px;">b. as a result of primary obstruction of the outlet toward the bowel:</p> <p style="margin-left: 40px;">(a) by primary organic stenosis of the pylorus or folding of the mucous membrane (Tilger);</p> <p style="margin-left: 40px;">(β) from abnormal position, fixation, or kinking of the adjacent bowel by short mesentery, lig. hepato-duodenale, lesser omentum, etc. (Mayer, Schotten, Pitt) after foetal inflammations.</p> </td> <td style="vertical-align: middle; padding: 0 10px;"> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Primary spasm.</p> </td> <td style="vertical-align: top;"> <p>A reflex spasm from the gastric mucous membrane, produced by erosions and fissures, dyspepsia, or overfeeding (Pritchard), hyperchlorhydria (Knöpfelmacher)—from other sensory zones, as phimosis (Biedert);—on the basis of hereditary nervous predisposition (Freund and others);—in foetal life, from developmental deficiencies in the nervous system which allow the two segments of the stomach to act antagonistically instead of in harmony (Thomson);—as a result of delayed adaptation of the stomach to its digestive functions.</p> </td> </tr> </table> | <p>A. An exercise hypertrophy, the result of primary spasm (Thomson).</p> <p>B. A compensatory hypertrophy following stenosis:</p> <p style="margin-left: 20px;">a. as a result of primary spastic stenosis;</p> <p style="margin-left: 20px;">b. as a result of primary obstruction of the outlet toward the bowel:</p> <p style="margin-left: 40px;">(a) by primary organic stenosis of the pylorus or folding of the mucous membrane (Tilger);</p> <p style="margin-left: 40px;">(β) from abnormal position, fixation, or kinking of the adjacent bowel by short mesentery, lig. hepato-duodenale, lesser omentum, etc. (Mayer, Schotten, Pitt) after foetal inflammations.</p> | <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Primary spasm.</p> | <p>A reflex spasm from the gastric mucous membrane, produced by erosions and fissures, dyspepsia, or overfeeding (Pritchard), hyperchlorhydria (Knöpfelmacher)—from other sensory zones, as phimosis (Biedert);—on the basis of hereditary nervous predisposition (Freund and others);—in foetal life, from developmental deficiencies in the nervous system which allow the two segments of the stomach to act antagonistically instead of in harmony (Thomson);—as a result of delayed adaptation of the stomach to its digestive functions.</p> |
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ETIOLOGY.—There is a tendency to divide the etiology of the cases of hypertrophy from those of spasm, although this division does not seem to be very satisfactory. Race is supposed to play some rôle in the predisposition to hypertrophy, since these cases are reported exclusively from Anglo-Saxon and Scandinavian countries. Pylorospasm, on the other hand, is met with in all countries. As regards sex, it would seem also that

stomach several hours after the feedings are important. As regards the diagnosis between hypertrophy and pylorospasm, it would seem at the present time to be impossible to determine at the outset which condition is present. The exact diagnosis must await the results of medical treatment. Even then it is possible that cases of hypertrophy, if of mild grade, may end in recovery without surgical intervention.

Differential Diagnosis.—Pyloric stenosis must be distinguished from gastric indigestion with severe vomiting. The important signs indicating stenosis are the absence of bile from the vomited matter, and palpable pylorus. In very rare instances pyloric stenosis might be confounded with congenital atresia of the pylorus or congenital stenosis or atresia of the duodenum. In these cases, however, the symptoms would exist from birth.

PROGNOSIS.—The prognosis of pyloric stenosis varies with the time of onset and with the severity of the symptoms; the later the vomiting begins, the better the prognosis, as a rule. Inasmuch as all grades of stenosis may be present, and since even with hypertrophy there may be varying grades of spasm, the ultimate outcome of any particular case must depend upon the success of the various medical, dietetic, and surgical measures used in treatment.

TREATMENT.—Medical.—Since in any given case it is impossible to know at the outset whether one is dealing with a case of hypertrophy combined with spasm or a case of spasm alone, the aim of conservative treatment must be to prevent all irritation of the pyloric end of the stomach by food remains or by the acrid products of gastric indigestion. Moreover, in addition to these dietetic measures, treatment should be directed to removing acid mucus, to rendering the pylorus less sensitive, and to relaxing whatever spasm may be present.

As to the *Diet*, breast milk is of course to be preferred; but inasmuch as many of the cases arise in breast-fed infants, it is evident that some modification of the milk or of the method of feeding is advisable. The nursings should be for a shorter period of time than usual in a baby of the given age, and the intervals between the nursings should be long, in order to allow the stomach to complete the necessary changes in the milk and to be thoroughly evacuated. The breast milk should be diluted if its fat percentage is 3 or over. This is best done by giving lime water or some mucilaginous or carbohydrate gruel before the feedings.

If it is impossible to obtain breast milk, modified cow's milk or goat's milk of low fat percentage, prepared with a thin cereal gruel rendered alkaline by lime water, and then peptonized, is the best substitute. The proprietary foods that are rich in maltose are apt to give rise to gastric fermentation and increase the trouble. Sutherland advises the use of raw beef juice and the administration of carminative waters between the feedings.

Drug Treatment.—Heubner favors the use of atropine or morphine given by rectum. He believes that the atropine is of greater efficiency than the morphine.

Neild advises the use of small doses of opium (one-eightieth of a minim of laudanum) diluted and given by mouth a little time before each feeding, with the idea of relaxing the spasm. On the other hand, Sutherland does not believe that morphine is of value.

Lavage of the stomach, normal saline solution or bicarbonate-of-sodium solution being used according to Still's proposal, has seemed of advantage in numerous instances. It probably is of most benefit in cases that show an excess of mucus in the vomitus. At times a hard mucus plug will be washed out, and after such treatment the amount of food passing into the intestines will be increased.

Warm compresses upon the abdomen or poultices applied to the epigastrium are undoubtedly of the greatest value. They should be used in every case.

Surgical Treatment.—Operative treatment should be a last resort, since the mortality of operated cases is from 40 to 70 per cent. About this condition, as about most others which may demand operation, the surgeons make the assertion, with some justification, that the mortality rate would be much lower if the cases were operated upon earlier. The decision to operate should be made before the child has become badly debilitated. This means that the dietetic and medical treatment should

be thorough and that careful observations should be made to determine whether the child is making progress in the right direction.

Stern in 1897 was the first to operate, unsuccessfully, by gastroenterostomy on a patient six weeks old. Abel, in November, 1898, reported the first successful operation—a gastroenterostomy on a male infant eight weeks old. The surgical procedures which have been used are Loretta's pyloric divulsion, pylorotomy, pyloroplasty, and gastroenterostomy. Pyloric divulsion is often impossible because in true cases a proper instrument for stretching the pylorus cannot be inserted. Pylorotomy likewise is very difficult and uncertain, so that the methods of choice are pyloroplasty and gastroenterostomy. Of these the former takes less time and involves less exposure. According to Fisk it is to be preferred for physiological, anatomical, and surgical reasons. In some cases, however, the thickening is so great and the pylorus so firm that the operation is impossible. In those cases in which it can be done, it is undoubtedly the best procedure. Gastroenterostomy is done by connecting the posterior wall of the stomach with a loop of the jejunum, employing either suture or a Murphy button. Recently, in a discussion of the subject, Abbe, of New York, proposed a new method, namely, the division of the muscular fibres of the pylorus in a longitudinal direction down to the submucous layer. He believed that this would prove a simple and effective means of removing the firm contraction without any appreciable shock, or danger of peritonitis. According to statistics collected by Pfaundler, gastroenterostomy was done in 24 cases with cure in 11. Pyloroplasty was done in 15 cases with cure in 7. Loretta's divulsion was done in 11 cases with cure in 6. The general mortality of the operation is probably about 60 per cent. In regard to special details of the operation the literature of the subject should be consulted, especially the articles by Cautley and Dent.

Shaw and Elting give a very good table of the medical and surgical cases in their paper in the *Archives of Pediatrics*, 1904, p. 892.

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The bibliography of the subject has grown to be quite extensive. A list of the references arranged chronologically may be found in Dorning's article, *Archives of Pediatrics*, 1904, p. 681, and an alphabetical arrangement may be found in Fisher's article in the same journal for 1906, p. 241.

Linnaeus E. LaFétra.

RADIUM.—Radium is a radioactive substance supposed to be a new element. Professors Curie and Demarcay have isolated in small quantity and tested what they consider to be pure radium, obtaining from their samples a characteristic spectrum, and have determined the atomic weight to be 225. On account of the rarity and great difficulty and cost of isolating radium it is used in the form of a bromide or chloride.

Discovery.—The discovery of radium is due to investigations upon radioactive substances. In 1896 M. Henri Becquerel, member of the Institute of France, reported the discovery that uranium gave off radiant energy having many of the properties exhibited by the radiations from x-ray tubes.

The radiations from uranium were given the name of Becquerel rays, from the distinguished scientist who discovered them. These rays have the property of discharging electrified bodies and of producing chemical changes in the silver salts ordinarily used in photography, in these respects being similar to the x-rays.

Uranium was first discovered in 1789 by the German chemist Klaproth, and named by him from the planet "Uranus." Uranium, though widely distributed, is never found in large amounts, and forms several minerals. The most common of these is uraninite, commonly known as pitchblende. It contains about eighty per cent. of uranium. The pitchblende which contains the largest amount of radioactive substances is the Bohemian pitchblende;

but it is also found in Saxony, Cornwall (England), and in Colorado (United States).

Professor Curie and Mme. Curie, in investigating the Becquerel radiations from uranium found that some samples of pitchblende, from which the uranium had been extracted, gave forth radiations much more powerful than any they had found, having, in fact, four times the radioactivity of metallic uranium. They concluded that uranium being absent, the radiations were due to some unknown substance in the pitchblende, and following out this they discovered, in 1898, a substance to which they gave the name of "polonium." Polonium passes more rays through aluminum than uranium does, but these rays do not penetrate glass, are readily absorbed by minerals, and are cut off by thin paper. In the same year, following up the discovery of polonium, M. and Mme. Curie and M. Bemont isolated a second substance from pitchblende which possesses many of the chemical characteristics of uranium, but is much more powerful. To this they gave the name "radium."

Properties of Radium.—Radium is one of the most peculiar substances known to science, and produces phenomena which were hitherto unknown as existing in any chemical element or chemical combination: (a) It glows constantly with a visible light; (b) it gives off constantly a certain degree of heat; (c) it produces electrical effects similar to those produced by the x -rays; (d) it causes certain chemicals to fluoresce; (e) it reduces the silver salts ordinarily used in photography; (f) it transforms white into red phosphorus, and produces other transformations, such as changing the color of glass, porcelain, white paper, rock salt, etc.; (g) it has a distinct effect upon living tissue.

Nature of Radium Radiations.—The discovery of x -ray radiations and radium radiations has given rise to many ingenious theories, but experiments appear to show a distinct difference between radium rays and x -rays and the emanations from radium. Radium rays like x -rays pass through glass and substances opaque to ordinary light, while radium emanations are of peculiar character and appear to be more like a vapor. These emanations do not pass through glass, but settle upon all objects with which they come in contact, and like vapor of water may be condensed by extreme cold. The emanations from radium produce radioactivity in other substances, the result being, so far as is known, that all substances may be rendered radioactive through the influence of radium emanations. Substances so rendered radioactive present to a degree all the phenomena which radium itself presents, and when so charged retain the properties of radium for varying periods of time. The Curies have determined that substances thus rendered radioactive retain their induced radioactivity very much longer when guarded in a small enclosure through which the emanations cannot pass. In such cases the induced radioactivity diminishes one-half every four days, while in substances not so guarded it diminishes one-half every twenty-eight minutes.

Nature and Measurements of Radium Radiations.—There are three entirely distinct types of rays emanating from radium. These are known as the " α ," " β ," and " γ " rays. The α rays are the least penetrating, losing about one-half of their intensity if passed through aluminum 0.0005 cm. in thickness. The β rays are much more penetrating and much longer, and correspond in every particular to the characteristics of cathode rays. They are readily deflected by a magnet, discharge electrified bodies, etc.

The γ rays are the rays possessing the greatest penetrating power. These rays will produce radioactivity through the air at a distance of four feet or more, and are so much more penetrative than α rays that they require aluminum 8 cm. in thickness to reduce their intensity one-half.

The radioactivity of radium compounds is measured in terms of uranium, this element being taken as a standard. Professor Curie states that pure radium possesses one million times the radioactivity of uranium, but from

the rarity of the substance and the difficulty of obtaining it in a pure form, the radium compounds which have so far been available for experiment have rarely been above a radioactivity of 7,000. The quantity of radium and radium compounds so far produced has been exceedingly small and the cost is very great. Professor Curie states that it would take five thousand tons of uranium residue to produce a kilogram of radium at a cost of about \$2,000 per ton.

Heat-Producing Properties.—Radium has the remarkable property of maintaining its temperature at about 1.5° C. above its surroundings. Heat production like light production from radium appears to be made without any change in the radium and without any loss of weight. This remarkable force production as exhibited by constant heat production can be appreciated when it is understood that radium radiates enough heat to melt more than its own weight of ice every hour, and to continue, so far as is known, this force production for an indefinite period.

Light and Fluorescence.—When a tube containing radium is viewed in the dark it is seen to emit a distinctly visible light. The light emitted is of uniform quality and is produced indefinitely, and, so far as is known, without any change in the radium itself. When the rays from radium are directed upon the double cyanide of platinum and barium, tungstate of calcium, and certain other chemicals which fluoresce under the action of the x -ray, the radiations from radium cause these substances to glow with a visible light; the properties of the radiations from radium in this respect being like those from the x -rays. A sufficient quantity of radium has never been obtained to allow of the practical use of the fluorescence so obtained in the way in which the fluoroscope is used with x -rays, but it is possible that with a sufficient quantity of radium a fluorescence equal to that of the x -rays could be produced.

Photochemical Effects.—When the rays from radium are directed upon a sensitized photographic plate from which all ordinary light is excluded by having the plate enclosed in a light-tight envelope, the silver salts are reduced, and an effect similar to that produced by the x -rays is obtained.

This photo-chemical effect appears to be identical with that produced by the x -rays, except that either from the radiations from radium being less powerful in photochemical effect or from a sufficient quantity of the substance not being used, the rays have not as great penetrating power. Exposures of long duration produce outlines of the human hand with but faint indications of the bones.

Like the fluorescent effects of radium the photochemical effects have not as yet been made of practical value. Practical results may, however, be possible, provided radium can be obtained in sufficient quantities and its action can be properly controlled.

Vitochemical Effects.—The effect produced by the radiations from radium on living tissue are most remarkable. These effects, in certain ways, resemble the effects produced by x -rays, but appear also to have peculiar properties which, so far, have not been found to be produced by x -rays. Radium rays, like x -rays, are capable of producing "burns." The discovery of this effect of radium was made by Professor Becquerel, who, when journeying from Paris to London, carried in his waistcoat pocket a small tube of radium. About a fortnight later the skin under the pocket began to redden and fall away, and finally a deep and painful sore formed which was several weeks in healing. Like the burns produced by the x -ray these pathologic effects of radium radiations do not appear until several days after the part has been exposed. Many other important vitochemical effects are produced by the peculiar force thrown out from this remarkable substance. Becquerel found that if seeds were exposed for a long time to the emanations from radium their germinating power was destroyed.

M. Banysz, in experiments in the Pasteur Institute, found that the emanations from radium produced re-

markable effects upon rabbits, guinea-pigs, and other small animals. These experiments show that radium has the remarkable power of so interfering with organic processes as to inhibit growth and even destroy life. A small amount of radium suspended over a cage containing mice will, after a few days, cause loss of hair and blindness, followed later by death. The same experimenter reports that exposure to the radiations from radium will cause arrest of development in certain lower organic forms. He exposed the larvæ of *Ephestia kuehniella* in a glass flask to the emanations from radium for a few hours. After a few weeks it was found that most of the larvæ were killed, but that a few had escaped the destructive action of the rays by crawling into distant corners of the flask where they were still living, but living as larvæ; whereas in a control flask similar larvæ had changed into moths.

M. Bohn has shown that radium may so modify various lower forms of life as to produce "monsters," and he has caused remarkable deviations from the original type in tadpoles exposed to radium emanations.

The vitochemical effect of radium seems to be particularly expended upon the skin and subcutaneous tissues and the nervous system. Thus, Danysz reports that the application of a tube containing a salt of radium to the skin produces an ulcer in from eight to twenty days. A few moments' application produces congestion of the human skin. When applied to the skin of a rabbit destruction of the epidermis follows, but when applied under the skin there is only a feeble reaction on the epidermis. Danysz found that when tubes containing radium were introduced into the intestines and serous cavities of guinea-pigs very little effect was produced, but its action was noted upon the nerve centres of all animals subjected to experiment. This action, however, was comparatively feeble in those whose osseous tissues protected the nerve centres. Application of tubes containing the salt to the cranium caused paresis, ataxia, and convulsions, followed later by death.

Professor Curie introduced a few milligrams beneath the skin of a mouse over the vertebral column, causing death of the mouse in three hours.

The rays of radium have a direct effect upon the optic nerve. This was shown by Giesel, who found that when radium salts were brought near the closed eyes a sensation of light was produced. This is attributed by Hammer to phosphorescence of the humors of the eye and also to effect upon the nerves of the retina. Prof. M. Javal proposes a diagnostic use of this phenomenon, and suggests that blindness with alteration of the retina can be distinguished from that due to glaucoma or corneal opacity, because patients with the latter condition see rays from radium as well as those of sound vision, while patients who have alteration of the retina have no sensation of light when a salt of radium is placed near the eyes.

Therapeutic Uses.—The vitochemical action of radium is so like that of the α -rays that its use for the cure of conditions for which the α -rays have been used was at once suggested. Experiments seem to show that the vitochemical action of the rays of radium are much more powerful than those of α -rays. There seems every probability, when radium can be produced in sufficient quantity and its action properly controlled, that it will be a valuable therapeutic agent. So far, its use has been mainly confined to the treatment of lupus, epithelioma, and superficial skin diseases. Favorable reports of results of its use in these diseases have been given by a number of clinicians. Danlos reports a case of lupus of the face, exposed to the action of a salt of radium which had a radioactivity of 19,000 for from twenty to thirty-six hours, with the result of the disappearance of the disease and with the formation of a smooth, white cicatrix. Other clinicians have reported equally favorable results and have called attention to the good effect as shown by the smooth, soft, and white resulting scar.

For therapeutic use the radium compounds have in some cases advantages over the α -ray. In superficial diseases of the skin and mucous membrane these radium

compounds, being enclosed in small hermetically-sealed glass receptacles, can readily be employed as therapeutic agents. All that is necessary is to place the receptacles containing the compound in close apposition to the parts, so insuring a local action. Furthermore, radium compounds being permanent these glass receptacles can be used for an indefinite time in any number of cases, and this apparently with more surety of definite results, so far as tissue reactions are concerned, than can be obtained from the radiations from α -ray tubes.

William Cline Borden.

RHINOPHARYNGITIS MUTILANS.—*Definition.*—A peculiar destructive ulceration of the nasopharynx prevalent in certain limited areas in the tropics, without constitutional symptoms and usually running a self-limited course with a tendency to cicatrization. It is almost certainly infectious and quite probably contagious. Its specific cause has not been discovered.

History and Geographical Distribution.—Lesions similar to those which characterize this disease, and not to be accounted for by any connection with syphilis, tuberculosis, or leprosy, were mentioned in 1839 by Maxwell¹ who encountered them in Jamaica and believed them to be sequelæ of frambœsia (yaws). Following Maxwell in this belief, Numa Rot² described sixty cases which he encountered in a limited district on the windward side of the Island of Dominica, West Indies, as probably representing some late stage or sequel of yaws. C. W. Daniels,^{3,4} who encountered cases in Fiji, was the first writer to throw doubt upon their connection with yaws. Many observers who have had no familiarity with the condition and who have seen it only casually have confounded it with leprosy, tertiary syphilis, or localized tuberculosis. It was differentiated from these diseases and from yaws and described as a disease *sui generis* under the name *rhinopharyngitis mutilans* by the present writer, first in 1904,⁵ and again more fully in 1906.⁶ Since its specific cause is still undetermined, and since any of the gross lesions characteristic of rhinopharyngitis mutilans may be produced by some other disease, its differentiation may be said to rest at present almost entirely upon its peculiar and extensive prevalence in certain places, certain known endemic areas. The only regions of the world that are known at present to be endemic areas for this disease are Fiji, Guam, the Caroline Islands, and the Island of Dominica, West Indies. A study of the condition at first hand in any one of these endemic regions will soon convince the most sceptical observer that he is dealing with a peculiar pathological condition which, whatever it may be, is certainly *not* syphilis, nor tuberculosis, nor leprosy.

The patient's denial of any venereal history, a failure to demonstrate the *Treponema pallidum* in any isolated case of extensive nasopharyngeal ulceration, and failure of such a case to respond in a prompt and striking way to iodides afford no sufficient grounds for excluding tertiary syphilis. Nor is failure to demonstrate the bacilli of leprosy or of tuberculosis in any such single case sufficient to exclude those diseases. Articles dealing with rhinopharyngitis mutilans have been published recently by several writers of very limited acquaintance with it; by some who have never been in any of the places where it is known to exist and who confess to having had no experience of it at all. An isolated case of rhinopharyngeal ulceration in a negro from Panama,⁷ treated in New York, has been tentatively accepted as a case of rhinopharyngitis mutilans. From an extensive experience on the Isthmus, the present writer can state that the disease is unknown in Panama. Another case has been reported, with photograph, in the person of a confirmed leper, an inmate of a leper asylum⁸; and a third case, occurring in a white American adult, in which there was an acceptable history of syphilis contracted five years previously, and the lesions described were characteristic of that disease.^{9, 10} The reporting of such dubious cases as

these, while the etiology and differentiation of rhinopharyngitis mutilans are still a problem, tends only to obscure and confuse the subject. It is not likely, as has been pointed out before, that any progress will be made in solving this problem until it is undertaken by competent investigators working in one of the endemic areas.

Mink and McLean¹¹ have made a clinical study of eighty-one cases in Guam and tabulated them in a valuable report. It is to be regretted that, owing to lack of familiarity with the Spanish language, these writers should have mistaken a common Spanish adjective, *gangosa*, meaning "nasal-voiced," for a substantive, and employed it as a title for their article and a name for rhinopharyngitis mutilans. Stitt has followed them in this error which, beside its essential incorrectness, tends to introduce confusion into nomenclature.

Etiology.—The disease affects persons of all ages; and from the fact that several members of the same family are often seen to be affected with its peculiar lesions and to be otherwise in good health, the disease would appear to be contagious. It may not improbably be caused, like the blastomycetic dermatitis, or like mycetoma, by the local invasion of a parasitic organism. No cases that can be regarded as authentic have yet been reported in others than Malays and negroes.

Clinical Course.—The patient, if seen early, as few are, complains of sore throat. On examination, an ulcer is seen on the back of the pharynx, on a faucial pillar, or on the free edge of the soft palate. It is superficial, movable, covered with a thin, dirty, greenish-gray or brownish-gray pellicle of slough. This is apparently the initial lesion. The pellicle breaks down and leaves an ulcer which steadily increases, advancing up the throat into the posterior nares. The disease begins in the soft parts, but, after reaching the soft palate and eating its way through its entire thickness, attacks the bone of the palate and nasal septum, finally destroying them. The serpiginous ulceration, after being thus active and advancing for months or years, usually arrests itself at this stage, the ulcers healing, and leaves the victim with no septum, the nasal cartilage and skin fallen in, the nose and mouth one large cavity. The faucial opening is apt to be narrowed by cicatricial tissue, making deglutition difficult. The disease rarely advances downward from the pharynx, the larynx is only exceptionally affected and phonation remains normal, though, owing to palatal destruction, the quality of the voice is deranged and articulation is defective, the speech being affected precisely as in any case of cleft palate. There are no constitutional symptoms. The patients, if they were so in the first place, remain well-fleshed, strong, and able to follow their usual avocations. The disease process having ceased, the patient carries its marks, in palatal bone destruction and pharyngeal scar tissue, to old age. In a few of the cases, fewer than ten per cent. of them, the process is not arrested at this stage, and the ulceration destroys the cartilage and skin of the nose and advances upon the face. In about twenty-five per cent. of the cases (21 out of the 81 cases in Mink and McLean's series) the process extends up through the nasal ducts into the conjunctivæ, where it produces in the eyelids granulation tissue at first, scar tissue afterward, with ultimate inability to close the eyes, keratitis and blindness frequently resulting. The tongue appears never to be involved. The upper lip usually remains as a bridge, in cases in which the nose has been destroyed, and through the anterior nares one looks into the mouth and throat. Even in these most extensive and aggravated cases, however, there is no evident impairment of the general health.

Diagnosis.—Rhinopharyngitis mutilans must be distinguished from *leprosy* by the tendency to a spontaneous cure, the absence of leprosy lesions elsewhere, and the absence of the *lepra bacillus*; from *tuberculosis* by the non-existence of tuberculosis in other parts of organs,

the infrequency of downward extension and laryngeal involvement, the peculiar tendency to extension through the nasal ducts and involvement of the eyelids, and the absence of the tubercle bacillus in the lesions; from *acquired syphilis* by the absence of any signs or history of primary or secondary syphilis and by the onset of the disease in infancy and childhood; from *hereditary syphilis* by the absence of any of the signs of that disease and by its incidence in the healthy children of healthy parents. In its endemic areas where its prevalence is a familiar fact the diagnosis presents no difficulty.

Prognosis.—In natives who are well provided with the necessities of life, who live in comparatively good hygienic surroundings, and who can be kept under observation and treatment, a favorable prognosis can be given for most cases. In children of five years or less the onset of the disease is apt to be sudden, and accompanied by moderate or high fever, and to result in death within a very few days. The term "fulminating" has been applied to these fatal cases in infancy and childhood.

Treatment.—Whether or not the process be due to some specific infection, it is at any rate difficult to arrest, especially in cases where the serpiginous ulceration has advanced into the nares and is difficult of access. In the few cases seen early, when the disease is limited to the pharynx, and in the still rarer cases in which its beginning is visible in the anterior nares, cauterization with the silver nitrate stick may be practised. Spraying with hydrogen peroxide is effective in removing the sloughing surface of the ulcer and developing a healthy granulating surface. Granulation may be stimulated by the application of tincture of iodine. The use of a detergent and stimulating gargle is beneficial. In some cases iron and tonics may be useful. Potassium iodide internally in full doses is usually well borne and seems to do good in some cases.

J. F. Leys.

¹ Observations on Yaws, Prize Essay, Edinburgh, 1839.

² Yaws: Its Nature and Treatment, London, Waterlow & Sons, 1891.

³ Selected Essays and Monographs, New Sydenham Society, London, 1897.

⁴ Brit. Jour. Dermat., London, 1896, viii., 426.

⁵ Report Surgeon-General, U. S. Navy (1904-05), 1905.

⁶ Jour. Tropical Medicine, London, Feb. 15th, 1906, ix., 47.

⁷ Jour. Cutaneous Diseases, New York, January, 1906.

⁸ Report Surgeon-General, U. S. Navy, 1906, p. 176.

⁹ U. S. Naval Medical Bulletin, vol. i., No. 2, July, 1907, p. 96.

¹⁰ Philippine Jour. Sci., vol. ii., No. 4, August, 1907, p. 387.

¹¹ Jour. Amer. Med. Association, Oct. 13th, 1906, xlvii., 1166.

ROENTGEN RAYS, THE PATHOLOGICAL CHANGES PRODUCED BY.

—In the twelve years that have elapsed since Roentgen announced the discovery (November, 1895) of the rays that now bear his name, clinical medicine has witnessed a remarkable application of the new physical agent along diagnostic and therapeutic lines. Practically every branch of clinical medicine has seen a vigorous utilization of the rays, either experimentally or empirically; and, as is usually the case with a new discovery, over-zeal has played a very important part in the prominence given to this new therapeutic agent. Without any actual knowledge of the effects of the rays upon the human organism, such as could be gained from animal experimentation, great numbers of practitioners took blindly into their hands an agent that we now know to be one of great power, in so far as its action upon the cells of the body is concerned. As the result of such an empirical use there has gradually accumulated a large amount of clinical evidence of tissue-changes produced by Roentgen irradiation, some of these tissue-changes being of a severe or dangerous nature, while others are of definite therapeutic value. To painful experience rather than to the results of experimental work do we owe the chief part of our knowledge concerning the action of the rays upon the skin and its structures, the sexual glands, etc.

In the case of some of these changes the delay as to

their recognition was the result of the fact that they either manifested themselves at a late period after the treatment, or were of such a nature that for a long time their association with the cause was not evident. Thus the sterility occurring in Roentgen-ray operators existed for a long time before its relationship to the rays was recognized. For some time after the introduction of the rays into clinical work the doubt was expressed by numerous workers in this line as to the ability of the rays to produce any effects upon the organism other than those of a local nature. It had early been discovered clinically that the exposure of the skin to the prolonged action of the rays might be followed by depilation associated with degenerative and inflammatory changes that were regarded as somewhat analogous to severe burns; but it was affirmed on many sides that the rays did not affect the internal organs. Naturally the first pathological studies of the effects of Roentgen irradiation were concerned with the changes occurring in the skin structures in the so-called "burn." These studies were not very extensive, nor did they excite much interest. The field apparently did not seem to be an attractive one to pathologists, probably for the reason that the clinical use of the rays was so largely empirical and the therapeutic results so doubtful or contradictory. Consequently very few experimental investigations as to the effects of Roentgen irradiation were carried out during the first six years of clinical work with the rays. Not until the remarkable symptomatic cures of leukæmia due to x -ray treatment were reported by some workers was the experimental study of the changes following Roentgen irradiation begun in earnest, numerous important contributions being then made to our knowledge upon the subject. As a result the last four years have seen a distinct change in the attitude of clinicians toward the question. The power of the rays to produce important changes in deep-seated organs, to affect the general metabolism of the body, and to give rise to conditions of toxæmia is now generally recognized; and, in recognition of the dangers attending their use, operators are now protecting their own bodies and employing much greater care in the diagnostic and clinical use of this powerful agent.

An analysis of the literature concerning the effects of Roentgen irradiation upon living tissues shows that observations of such action have been made in the case of the majority of the organs and tissues. It will be convenient, therefore, to class these effects according to the part involved.

General Effects.—Numerous cases have been reported of general disturbances resulting from Roentgen irradiation, in the form of such symptoms as fever, headache, dizziness, insomnia, restlessness, vasomotor disturbances, cardiac palpitation and irregularity, gastric pain, disturbances of appetite and digestion, etc. Profound symptoms of intoxication occasionally follow exposures, even when these are brief. Edsall has seen death result in two cases following one exposure, and a severe illness in a third case. Such a severe general reaction is most likely to occur in an individual suffering from anæmia, nephritis, or other toxic condition. These general symptoms are of the nature of an intoxication, and the condition is now generally spoken of as the x -ray toxic reaction. Aside from direct damage to the nervous or circulatory systems by the rays, the general symptoms partake of the nature of a proteid intoxication: that is, of an intoxication due to the products of protein disintegration. Such a destruction of nucleoprotein we know takes place throughout the irradiated portions of the body, particularly in the spleen, bone-marrow, and lymph-nodes. Evidences of this destruction are seen in the urine in a greatly increased total nitrogen output, with a relatively large output of uric acid, purin bases, and phosphates. Following this severe disturbance of metabolism there may be added a secondary intoxication due to injury to the excretory organs, the kidneys in particular. In the case of small animals exposed experimentally a continuous ex-

posure of two hours or longer causes death within ten to twelve days with symptoms of a severe general intoxication.

Skin.—Irradiation of the surface of the body causes, after prolonged or repeated exposures, an individual form of dermatitis ("burn"), characterized by a gradually developing hyperæmia and severe pain, burning and itching, and pigmentation. If the exposure has not been too severe the changes in the skin may go no further, the hyperæmia disappears slowly, the epidermis desquamates, and there is a slow return to an approximately normal condition. The affected part is usually less elastic than normal and shows a tendency to crack or to become secondarily infected. The area may become excessively pigmented or the normal pigment may be lost. The hairs are shed and the finger-nails become thinner or may also be lost. Various stages and degrees of x -ray dermatitis may be called out in different individuals by apparently the same degree of exposure. Repeated slight exposures may cause no other change than excessive pigmentation or a loss of the hair. A re-pigmentation of white hair has been observed after irradiation. An erythema followed by eczema has been seen to follow irradiation not only in the portions of the skin directly exposed but also at some distance from these.

In more severe cases, after extended exposure, the skin becomes dark-red and oedematous with the formation of blebs and exfoliation of the epidermis, and an ulcer results which shows but slight tendency to heal. Secondary infection may occur and the lesion become gangrenous or suppurative in character. In spite of all treatment extensive destruction of the affected region may take place; and amputation may be rendered necessary or death may result. In a number of cases squamous-celled carcinoma has been observed to develop in a chronic x -ray burn and the patient has finally succumbed to the neoplasm.

Since the changes in the skin were the first ones recognized clinically as due to the action of Roentgen rays, they were also the first ones to be studied microscopically and experimentally. Marcuse, in 1896, was the first to study the changes in the hairs occurring in a case of Roentgen-ray alopecia and dermatitis. He found the roots of the hairs to be fibrillated, the sheath swollen, the basal cupping absent, and the characteristic structure of the hair-shaft and medulla destroyed. In 1897 Gilchrist examined pieces of skin taken from the fingers of a case of x -ray dermatitis and found the microscopic picture of a chronic dermatitis with excessive pigment formation. Oudin, Barthélemy, and Darier studied the changes occurring in experimental x -ray alopecia in guinea-pigs, and noted a nearly complete atrophy of the hair-structures and glands, but no changes in the blood-vessels or nerves could be ascertained. Kibbé in the same year examined microscopically a piece of skin excised from an x -ray burn, and noted degeneration of the nuclei of the epithelium of the lower layers of the epidermis with evidences of a slight inflammatory reaction in the corium. In 1898 Unna found that the collagenous tissue of an irradiated area showing reddening and pigmentation no longer reacted to stains in a normal manner but had become basophile. Jutassy, in 1899, confirmed experimentally in rabbits the changes found by Oudin, Barthélemy, and Darier.

Gassmann from a careful microscopic study of a deep x -ray ulcer came to the conclusion that the essential cause of the ulcer and its slow healing was to be found in a marked degeneration and vacuolization of the intima and muscularis of the vessels of the cutis and subcutis. Lion, in 1901, also noted vascular changes in the form of vacuolization and endothelial proliferation in the vessels of irradiated skin and in the neighborhood of x -ray ulcers. A more important study of the effects of Roentgen rays upon the skin was made in 1902 by Scholtz. Using young pigs he found that irradiation of the skin caused primarily a degeneration of the

cellular elements, while the connective-tissue elements were only secondarily involved in the reactive inflammation. Numerous other writers (Rudis-Jicinsky, Gassmann, et al.) have made contributions to our knowledge of x-ray burns and ulcers. Some of these have attributed the lesions to changes occurring in the blood-vessels or nerves; but the present trend of opinion is to the effect that the cellular elements, particularly the epithelium of the hair-follicles and the lower layers of the epidermis and the wandering cells, are damaged or killed by the rays, while the connective-tissue, elastic tissue, blood-vessels, and muscle are apparently not injured primarily to any great extent, but are involved in the reactive inflammation. The destruction of the rudimentary lymph-nodes in the skin may account for the slow development of the inflammatory reaction in some cases; in others there is time between the exposures for a regeneration of the injured cells. After repeated injury the regenerative power may be lost and with the death of the cells the x-ray ulcer is gradually formed. Its slow healing is due to the damage to the nerve-trunks, blood-vessels, etc., of the neighboring parts.

Circulatory System.—Changes in the heart-muscle due to irradiation have not yet been described. Cardiac disturbance following prolonged or, rarely, even short exposures has been reported. Irregularity, palpitation, and even a fatal cardiac insufficiency have been observed in these cases. It can not be said at the present time whether these symptoms are the result of the action of the rays on the heart-muscle or the nervous system, or on both.

Vacuolization and degeneration of the endothelium of the superficial blood-vessels have been noted in x-ray lesions of the skin. Similar changes have also been found in deeper blood-vessels in cases treated over a long period of time. Obliteration of the vessel-lumen, thickening of the intima, hyaline change, etc., also occur in such vessels. According to Halkin the earliest changes perceptible in irradiated skin are to be found in the capillaries. On the third day after the irradiation these are dilated, by the seventh day the endothelial cells are swollen, and by the twelfth day they show vacuolizations.

Blood.—The action of Roentgen rays upon the blood has been studied by a number of writers. Baermann and Linser could find no change in irradiated blood and red corpuscles. Irradiation of the corpuscles did not affect the hæmolytic action of hæmolytic sera, nor did it alter the action of non-hæmolytic sera. The irradiation of sera caused, however, a loss in hæmolytic power toward non-irradiated red corpuscles. Milchner and Mosse confirmed the resistance of the red cells to irradiation. On the other hand, Joseph and Kurpjuweit found well-marked changes in the red cells taken from a leukæmic patient and exposed *in vitro* for thirty minutes. Grawitz noted the diminished resistance to hypertonic solutions of the white cells from a case of irradiated leukæmia. Aubertin and Beaujard noted that in leukæmia the white cells increased in number immediately after the irradiation and then fell below the original number. When repeated exposures were given the primary increase did not occur, and the fall took place immediately. Gramegna and Quadrone showed that the red corpuscles, aside from a slight decrease in physical resistance, were not altered by irradiation. The hæmoglobin was not affected. Both the specific density and the coagulability of the blood were increased. The mononuclear and polymorphonuclear white cells were diminished in number, and fragmentation and degenerative changes were noted in both nuclei and protoplasm. According to experimental investigations by Briganti-Colonna irradiation is capable of inhibiting leucocytosis, and in animals irradiated after the leucocytosis had reached its acme the number of white cells was diminished. The polymorphonuclears were chiefly affected. According to Lefmann the lymphocytosis occurring after injections of pilocarpine can be inhibited by irradiation.

In cases of myelogenous leukæmia repeated irradiations may reduce the number of the white cells down to normal, while the relative proportion of the different forms may be brought back nearly to the normal condition. A similar effect may be seen in lymphatic leukæmia, although the reaction is not so marked as in the myelæmic form. Cases have been reported in which under irradiation the blood-picture of leukæmia was transformed into that of pernicious anæmia. The writer has also seen a lymphatic leukæmia develop in a case of Hodgkin's disease in which frequent irradiations had greatly reduced the size of the cervical and axillary glands. According to Hynek cases of pernicious anæmia may be cured by irradiation as the result of the lymphocytolytic action of the rays upon the bone-marrow.

Blood-forming Organs.—The investigations of Heineke, Warthin, and others have revealed the remarkable action of x-rays upon the spleen, lymph glands, and bone-marrow. The rays have a selective action upon lymphoid, myeloid, and epithelioid cells, causing in these a nuclear disintegration, fatty or hydropic degeneration, and necrosis. Through prolonged exposures practically all the lymphoid tissue of the spleen may be destroyed, not only in small animals but also in the case of the human body. The destruction of lymphoid tissue is more marked in the spleen than in the lymph glands or bone-marrow. The cells chiefly affected by the rays are the small and large lymphocytes and the myelocytes. The polymorphonuclear cells are affected to a less degree. In the spleen the lymphoid cells may, after prolonged or repeated exposures, completely disappear from the Malpighian follicles, so that the latter appear as lightly-staining areas made up of large vacuolated epithelioid cells.

Even after one short exposure extensive lymphocytolysis may be seen in the spleen of the rabbit or guinea-pig. In white mice or rats exposed for half an hour and killed immediately, extensive fragmentation of the nuclei of the lymphoid cells of the spleen could be seen. When killed within two to eight hours after the exposure the disintegration was very marked; many fields containing nothing but "chromatin dust," all the lymphocytes showing more or less disintegration. After ten to fifteen hours the disintegrated chromatin becomes collected in clumps, phagocytes appear, and evidences of regeneration are seen. Nevertheless the effects of the irradiation last for some time and are not immediately followed by a return to the normal condition. Exposures of five hours or more cause great destruction of the splenic lymphoid tissue and regeneration is not manifest even when the animals live ten days after the exposure. All the animals exposed so long died within twelve days after exhibiting symptoms of severe intoxication. There is no latent period in the effects of irradiation. The damage to the lymphocytes may be seen microscopically fourteen minutes after the exposure and the disintegration of the nuclei continues for several days. The same changes occur in the lymph glands and bone-marrow and the free cells of the tissues and blood are likewise damaged or destroyed.

In the case of a human body a lymph gland may be completely destroyed by repeated irradiations. The first changes noted are nuclear disintegration and fatty degeneration of the cells. This leads ultimately to a complete necrosis of the lymphoid tissue, so that the gland may come to consist of a small area of granular debris surrounded by a thickened capsule showing inflammatory reaction. Regeneration or new-formation of lymphoid tissue may occur outside the capsule in the neighboring adipose tissue. The changes in the bone-marrow are of the same nature but are less marked. The lymphocytes and myelocytes present the same degenerative or necrotic changes. The nucleated red blood cells are apparently not destroyed, and only after repeated exposures is their number diminished. It is probable that their parent cells are destroyed, since ultimately all the elements of the marrow disappear. The disappear-

ance of the nucleus from the normoblasts is apparently hastened.

The atypical lymphocytes and myelocytes found in the spleen, lymph nodes, and bone-marrow in leukæmia, Hodgkin's disease, lymphocytoma, etc., are particularly susceptible to the influence of the rays, and great numbers of these cells may be killed during an exposure. In consequence there must be thrown into the circulation a great amount of products arising from protein destruction, and in its adjustment to this condition the general metabolism of the body must be greatly disturbed. Evidences of this disturbance are seen in the development of a condition of toxæmia with such symptoms as fever, vertigo, cardiac irregularity, gastric pain, diarrhoea, etc. The urine shows a great increase in the total nitrogen output. Repeated exposures increase this toxæmia and may lead to a fatal issue directly or through renal changes produced by the excretion of poisons. Large lymph glands may be quickly reduced in size, and on microscopical examination be found to be completely necrotic as the result of the destruction of the atypical lymphoid or epithelioid cells. In the case of the spleen large areas of necrosis may be produced. Blood-vessels in the neighborhood of such necrosed areas may rupture and fatal hæmorrhage result. The leucolysis produced by Roentgen irradiation persists for several days or weeks after the exposures. This persistent destruction of the white cells has been explained as being due to the formation of a "leucotoxin" and a number of observers has apparently demonstrated the presence of such a toxin in the sera of irradiated animals (Curschmann and Gaupp, Capps, Helber and Linser, Schmidt and Géronne, etc.). In the case of nephrectomized animals it has been shown that the leucolysis is more rapid and marked, hence the conclusion that there is a leucotoxin produced that is excreted by the kidneys.

The selective destruction of the Roentgen rays upon the white cells and their parent cells explains the symptomatic improvement seen in cases of leukæmia, etc., treated by irradiation (See Leukæmia, Treatment of, by Roentgen Rays, in the present volume). The limitations and dangers of such a treatment are obvious.

Sexual Glands.—Experimental exposures of the testes of animals show that the rays have a destructive action upon the epithelium of the seminiferous tubules as shown by disintegration of the nuclei, disorganization and desquamation of the cells. The basal spermatogonia are especially affected, as are also the derivatives of these cells. Many of the tubules may come to contain masses of cellular debris only. The production of spermatozoa is either greatly lessened or completely lost. Slight exposures even, in the case of the human testes, are followed by a period in which the semen shows either numerous dead or distorted spermatozoa or none at all. The interstitial cells appear to be unchanged. In some animals irradiated for several hours persistent priapism develops with a constant flow of seminal fluid containing clumps of dead spermatozoa. Gangrene of the penis and testis may result. The condition of experimental azoospermia may persist for many months after the exposure, even when this has been of slight degree.

In man numerous observations of oligospermia and azoospermia and sterility have been made in the case of workers in Roentgen laboratories. In fact it is now generally believed that the great majority of such workers under the conditions existing a year or so ago were or are still sterile. In the majority of cases no decrease in sexual power or desire has been noted and this has been explained by the lack of injury to the interstitial cells. In a few cases only have atrophy of the glands and a loss of erectile power been noted. Since the use of proper protection some of these previously sterile workers have regained their power of spermatogenesis; in others the condition still exists.

From the various cases reported it appears definitely proved that a patient may be rendered sterile by Roent-

gen rays without receiving direct irradiation of abdomen or perineum, even when the exposure is not sufficient to cause a dermatitis. A condition of sterility may persist for several years in radiologists with preservation of virility and sexual ability. The absence of spermatozoa in such cases does not indicate permanent sterility, since in some operators perfect protection from the rays has been followed by the return of spermatogenesis within four months.

A similar destructive action is exerted by irradiation upon the ovary. Numerous observations, both experimental and clinical, have shown that cells of the zona pellucida become necrotic and desquamate and that the ripe ova are killed. The primordial ova in some cases appear to be affected, in others not. Halberstaedter believes that the ovaries are much more sensitive to the rays than are the testes. He found that irradiation caused a great diminution in the size of the organs. Foveau and Courmelle observed cessation of the menses and atrophy of the ovaries in thirty cases of myofibroma of the uterus treated by irradiation. Other instances of sterility similarly produced in the woman have been reported.

Effects upon Development.—Bardeen found experimentally that irradiation causes premature death of spermatozoa. Eggs fertilized by spermatozoa exposed for a long period either do not develop, or give rise to monsters. He concludes that nuclear substance may be so altered by irradiation that after a latent period it will call forth abnormalities in development. An injury to spermatozoa by Roentgen rays may be of such a nature that the spermatozoa survive, and are capable of fertilization, but the ova fertilized by them develop into monsters. Hippel and Pagenstecher found experimentally that irradiation of the young embryos of rabbits killed the embryos, or in case they survived the young showed various malformations or died soon after birth. Abortion has been observed in the human female as the result of irradiation.

Bordier found that irradiation of silkworms caused the latter to become stunted in growth, darker in color, and less active. Such caterpillars produced smaller cocoons and the majority of the larvæ died; very few passed into the complete pupa state and none reached a perfect transformation into the moth stage. Perthes found that the irradiation of one wing of a young chick caused a marked inhibition of growth in the irradiated wing, so that it lagged far behind the other in its development, both the bones and the feathers being affected. He noted also that the irradiation of a healing wound caused a delay in cicatrization. Inhibition of growth due to irradiation has also been observed in man. Gilman and Baetjer found that the eggs of *Amblystoma* after irradiation gave rise to embryos showing no external mouths. Chicks developed in eggs exposed to the rays showed malformations of the occipital region and extremities, the feathers being abnormally distributed in patches over the body. On the other hand, Schwarz found that irradiation caused no inhibition of growth in the eggs of the sea-urchin.

Effects upon the Nervous System.—In animals exposed experimentally for relatively long periods of time, marked nervous symptoms rapidly develop. Blindness, paralysis, and coma are the most important of these nervous phenomena, and the question as to whether they are the result of changes produced directly upon the nervous tissues by the rays or are the result of the toxæmia arising from the disintegration of protein cannot be answered at the present time. Kienboch attributed the marked nervous symptoms to an inflammation of the central nervous system. Seldin found an intense injection of the meninges in white mice dying after irradiation, with paresis of the posterior extremities. In larger animals such changes were not found. Birch-Hirschfeld found in exposed rabbits a necrosis of the cells of the retina and a secondary atrophy of the optic nerves. Inflammation of the peripheral nerves is seen in and about x-ray lesions of the skin.

Kidneys.—Warthin has shown experimentally that transitory nuclear changes may be produced in the renal epithelium after slight exposures. After prolonged exposures these changes are more marked, appearing as a cloudy swelling associated with albuminuria. In the kidneys of human cases of leukæmia, lymphocytoma, and Hodgkin's disease treated by irradiation over relatively long periods of time he found marked degenerative changes and atrophy associated with extensive deposits of lime salts. As such changes are not found in untreated cases of these diseases it is fair to assume that they resulted from the treatment, probably from the excretion of poisons produced by continuous protein disintegration, but they may be also to some extent dependent upon the direct action of the rays. In common with Edsall the writer has called attention to the possible exacerbation of a nephritis by means of Roentgen-ray treatment.

Intestine.—Experimentally an increased formation of mucus can be produced throughout the intestine by repeated or prolonged irradiation. The writer has seen in a case of lymphatic leukæmia treated for a long period with abdominal exposures a most extraordinary formation of a mucoid material throughout the entire intestine, associated with a large mucocele of the appendix.

Up to the present time no thorough studies have been made of the effects of irradiation upon the *liver*, *pancreas*, *adrenals*, and the remaining internal organs. In the case of the *mammary gland* marked atrophy has been seen to follow irradiation; and atrophic changes occur in the *salivary glands* and *glands of the skin* as the result of repeated irradiations, even when these are of slight degree.

Effects upon Bacteria.—The experimental studies carried out by various investigators as to the action of the rays upon bacteria have given only negative results. No inhibitory or bactericidal action has been positively demonstrated. Nevertheless some clinicians assert that the rays have destructive action upon tubercle and lepra bacilli in the skin. These statements need further confirmation.

Protozoa.—Schaudinn found that amœbæ exposed to Roentgen rays soon became spherical and smooth, took up water, and became so swollen as to burst in an explosive manner. At the end of ten hours all the amœbæ exposed became converted into small heaps of granules. Joseph and Prowazek found that *Paramecia* and *Daphnia* showed a negative tropism toward the rays. In the case of *Paramecia* certain changes occurred that could be interpreted only as of the nature of an injury or exhaustion. On the other hand, Ross found that prolonged exposure caused no changes in trypanosomes.

Action upon Pathological Conditions.—The application of Roentgen irradiation to the treatment of neoplasms, lupus, leprosy, leukæmia, pseudoleukæmia, exophthalmic goitre, etc., is based upon the destructive action of the rays on young and growing cells. No specific curative action has been demonstrated; the cause of the disease is not affected; the cellular proliferation resulting from its action is alone influenced. Symptomatic cures rather than essential ones are therefore to be looked for in these conditions. Pathological proliferations, excess of growth, etc., are the conditions suitable for treatment by this method. It is contraindicated in conditions in which severe cellular damage has already occurred, or in conditions in which a stimulation of the regenerative powers of a tissue is desired.

The nature of the destructive action of the rays upon nuclei has been variously explained. No one of the different theories given is acceptable, however. Several writers assert that cholin produces in lymphoid tissues the same changes seen after irradiation, and they ascribe to the rays a "corrosive action." The disintegration of the chromatin of the lymphocytes or epithelial cells after irradiation remains an unexplained process, and an important field for investigation is here

opened up. The researches of the last few years have shown, however, the important fact that irradiation is not the harmless thing it was at first thought to be, and the reckless exposures for diagnostic purposes, once so common, are fast becoming a thing of the past. Operators have learned the necessity of protecting both themselves and their patients. The relation of the action upon the sexual glands to certain social and moral questions can only be hinted at here, and the same thing is true of the medicolegal questions arising out of the power of the rays to produce serious injuries.

Alfred Scott Warthin.

Literature.—The references given in this article can be found in full in the writer's paper published in the *Physician and Surgeon*, Detroit and Ann Arbor, 1907.

RONCEGNO.—Roncegno is situated in the Austrian Tyrol, not far from the Italian frontier, about twenty miles east of Trent which is on the line of railway between Innsbruck and Verona crossing the Brenner Pass. There is now a railway station at Roncegno on the Val Sugana line. The village has a charming situation in a valley 1,750 feet above sea-level, and is protected on the north by high mountains. The surroundings are most picturesque and attractive, but the life is said to be dull. The climate is fairly equable, May and September being the pleasantest months. Within a few miles of Roncegno is the resort of Levico, with springs of similar composition, a favorite spa for Italians.

The waters of both Levico and Roncegno are classed under the head of arsenical waters, or arsenic-and-iron waters, comparable with La Bourboule and Mt. Dore. Besides containing arsenic, however, of which there is .067 of arsenous acid to the litre, the Roncegno waters also contain very considerable amounts of the metallic sulphates, iron, manganese, aluminum, nickel, cobalt, and a notable amount of copper, namely, 1.27 of sulphate of copper per litre.

On account of its strength, the dose of this water is small and its effects have to be carefully watched. From one to four tablespoonfuls are drunk daily, the maximum amount being six tablespoonfuls.

Baths, douches, vapor baths, and inhalations are also employed, the water being largely diluted.

The source of this highly mineralized water is at a near-by mine, and from thence the water is conveyed to the baths in the village. It is at first turbid, but becomes clear on standing, a yellowish deposit collecting in the tanks. This deposit, made semi-liquid by means of steam, is employed as a "poultice bath," and is said to be beneficial in muscular rheumatism, chronic rheumatic arthritis, sciatica, and strumous joints. The effect of this application to the skin is said to be very irritating, and is apt to cause a papular eruption.

The diseases and conditions, besides those already mentioned, for which these waters are applicable, are, in a general way, those which would be benefited by the use of arsenical waters, or of arsenical and iron waters, such as anæmia, skin affections, the cachexia resulting from malaria, long convalescence from acute illnesses, and neurasthenia dependent upon an anæmic condition.

The accommodations are said to be fairly comfortable: there is a Kurhaus which accommodates one hundred and fifty persons, besides several smaller hotels. The season extends from May 1st to September.

Any one in search of arsenical waters, unless happening to be in the locality of Roncegno, would naturally select La Bourboule, not only on account of its ease of access, but as well on account of its more extensive and elaborate establishment and the greater certainty of obtaining suitable accommodations and skilled medical service. The amusement resources at La Bourboule are also much more varied, and altogether it would appear to be the more attractive place.

Edward O. Otis.

SAIODIN (Sajodin) is the calcium salt of mono-iodobenheic acid: a product of erucaic acid obtained from

rapeseed oil ($C_{22}H_{42}O_2$), Ca. It is a colorless, completely odorless, and tasteless powder. It is a chemical unit containing 26 per cent. of iodine and 4.1 per cent. calcium; insoluble in water, alcohol, and ether. On incineration it develops abundant iodine fumes. Exposed to light saiodin becomes yellow superficially without undergoing decomposition toward the centre of the mass. It is a product resulting from an effort to obtain a substitute for potassium, sodium, and strontium iodide, one which would possess the therapeutic value without the disturbing collateral effects. Iodipin had been introduced, a product obtained through the action of chloriodine on sesame oil; but containing both halogens it was applicable chiefly by subcutaneous injection because of its unpleasant oily taste. Saiodin contains no chlorine, is stable and tasteless. It is said to pass unchanged through the stomach and consequently without effect upon that organ; does not cause nausea or loss of appetite and slowly decomposes in the intestines from where it is utilized. Patients susceptible to the nasal, pharyngeal, and conjunctival symptoms of iodism are free from these collateral disturbances when using saiodin.

Saiodin is applicable in all cases where the iodides are employed, and in from 1 to 3 grams daily contributes to the organism less of iodine than when the iodides are given. It is recommended in tertiary syphilis, arteriosclerosis, asthma, chronic bronchitis, goitre, and glandular enlargements.

The dose is the same as that of potassium iodide.

John W. Wainwright.

SKIN AND ITS APPENDAGES: ANATOMY.—The skin, or integumentum commune, of the body acts as a covering and a protection for the deeper portions, besides being an organ of secretion, of excretion, of special sense—the sense of touch,—of common sensation, and the conservator of animal heat. Embryologically, it is developed from those two primitive layers of the blastoderm, the ectoderm and the mesoderm, which are formed by the cellular division of the impregnated ovule. The epidermis, or most external layer of the skin, is formed from the ectoderm, while a superficial portion of the mesoderm furnishes the remaining constituent parts—the corium, or cutis vera, and the subcutaneous or fatty tissue.

GENERAL CHARACTERISTICS.—When fully formed the skin can be regarded as a completely closed sac, which models itself so closely upon the portions of the body which lie immediately below it, that it allows their shape and configuration to be more or less accurately distinguished. This, naturally and to a great extent, will depend upon the amount of intervening fatty tissue. When the latter is present in excessive amount, symmetry and roundness of form are naturally lost.

The skin does not stop abruptly at the natural openings of the body. It is continuous at these points with the mucous membrane which clothes the cavities. At the nares, on the labia majora and minora, and on the external surface of the anus, the transition of the skin over to the mucous surface is gradual, but at the mouth, on the eyelids, and at the meatus urinarius, it is abrupt.

The integument is very variable in thickness. In general, it varies between 0.5 and 4 mm. ($\frac{1}{8}$ to $\frac{1}{2}$ in.), exclusive of the subcutaneous tissue. It is thinnest on the eyelids, and thickest on those portions which are subjected more especially to pressure, as on the palms of the hand and soles of the feet, or which serve as points of insertion for muscles, as on the upper lip, alæ nasi, etc.

Density and Elasticity.—It has been found that the skin possesses considerable solidity and very perfect elasticity. Sappey concluded from his experiments that a strip of skin 3 mm. long and 10 mm. broad was able to support a maximum weight of 12 kgm. (26½ lb.). The solidity was also in direct ratio to the thickness of the piece of skin used in the experiment. As mentioned, the elasticity is very perfect, but slight; a considerable amount of stretching may result from the application of a small weight, and complete rectification takes place after its

removal. The skin is not of uniform texture, but consists of bundles of connective-tissue fibres arranged like a net, between which are spaces of various sizes which are rhombic in shape. In these spaces there is found a cementing substance, and it is due to it and the enormous network of elastic fibres that the former are able to regain their natural shape after having been stretched.

Cleavage.—The cleavage lines of the skin were demonstrated by Langer. He pierced the skin with small, round awls in multiple places, and, after removal of the instruments, observed that the wounds which were made were linear. He then made series of them in rows and close together, and from uniformity in the direction of the long axes of a more or less greater number of them, he was able to conclude that the skin possessed complete linear cleavage over the greater part of the surface of the body. Not on all of it, however, for in some places, as on the forehead, on many points on the scalp, etc., the wound made was a triangular one, and he found that these occurred where two spaces met together which possessed linear cleavage in opposite directions. The explanation of the fact that the skin is, to a great extent, cleavable linearly, is to be found in the arrangement of the spaces between the bundles of fibres.

Tension.—Except upon the scalp, the palms of the hands, and the soles of the feet, the skin is, more or less, in a state of tension. When a portion is excised, it will be seen that it diminishes in size to such an extent that it will no longer cover the surface which has been laid bare. This cannot be ascribed entirely to the retraction of the borders of the wound, but is also due to the diminution in size of the excised piece, which is then no longer subjected to its former tension. Where the skin possesses linear cleavage, the tension is in the direction of these lines; but where this condition does not exist, it occurs uniformly in every direction in the plane of the surface. The tension likewise depends upon the movements of the joints and muscles, the amount of fat deposited in the subcutaneous tissue, and also upon morbid conditions, such as œdema, or upon the existence of pregnancy. In this latter condition the degree of tension may be so great that a permanent change may result in the direction in which the bundles of fibres run.

Color.—The color of the skin differs according to the individual, the race, and the age, and it also varies upon different portions of the body. It cannot be ascribed in certain races to climatic influences alone, since in the same zones people of different color are found, as in Africa, negroes, and in a corresponding portion of America, the much lighter colored Indians. The difference in color depends entirely upon the amount of pigment present in the rete Malpighii, where, under the form of granules, it is found especially in its lower layer or stratum basale. This is easily demonstrable in the skin of the negro two or three days after death, and before decomposition has set in. If the skin is, under such conditions, sharply rubbed, the epidermis is detached and rolls up under the finger, and the corium or true skin is seen to be of a dull white color. In the white race the color changes, within certain limits, in the various seasons of the year. When the skin is exposed to the heat and the sun in summer, there is an increase in pigment deposit and it appears darker, but this disappears and the whiter color returns in winter.

Under certain physiological conditions, such as pregnancy, there is likewise an increase in the amount of pigment in particular portions of the skin—the areola around the nipple, the linea alba, etc.—and this may in some instances be to an exaggerated extent. A large portion of this increase often disappears after the birth of the child, but a considerable amount usually remains. In the male the scrotum and penis, and in the female the vulva, are of a darker color than the rest of the skin. The pink or red color seen on certain portions of the body, as the cheeks, or induced by certain temporary causes, as those which produce flushing, is due to the blood in the vessels of the cutis. These latter becoming filled with blood its color is conveyed to the eye through

the epidermic covering. When venous congestion is present the color is more or less of a bluish tinge. In old age the skin acquires a more or less yellow color, due to the atrophic changes that take place in it, and also to the lesser amount of blood supplied to it.

The Folds and the Furrows of the Skin.—Many furrows are seen on the skin. Some are long and deep, others are short and shallow. The former are present to a great extent from birth, and are seen running in a transverse direction across the extensor and flexor surfaces of joints.

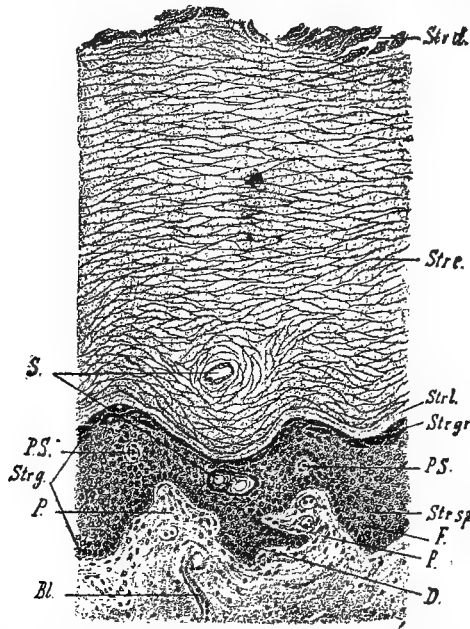


FIG. 5226.—Section of the Skin (epidermis and the papillary portion of the corium) on the Sole of an Adult Foot. Specimen hardened in a solution of picric acid and bichloride of mercury, and stained with hæmatoxylin and eosin. Magnified 90 diameters. (After Rabi.)
Str. d., Stratum disjunctum; Str. c., stratum corneum; Str. l., stratum lucidum; Str. gr., stratum granulosum; Str. g., stratum germinativum; Str. sp., stratum spinosum; F., fold of epithelium; D., glandular ridges; S., outlet channel of a sweat gland; P., papillæ; Bl., blood-vessel.

The latter are represented by the wrinkles on the face which develop with age. These latter are due partly to the diminished elasticity and turgescence of the skin, but they are induced more often by muscular contraction and stretching of the cutis.

The furrows around the joints are produced by the movements of flexion and extension. They are not able to overcome directly the tension of the bundles of fibres, which in this situation run transversely or obliquely across the joints; in consequence the fibre bundles are not stretched by the ordinary movements, but the rhomboidal spaces between them are. On one side of the joint their tension is in the direction of their breadth, while on the opposite side the fibre bundles are brought closer together. In this way the constant furrows around the joints are caused. Those which are due to muscular action, as the wrinkles on the forehead, etc., are produced in the same manner, the constant repetition of the movements finally effecting a permanent change in the arrangement of the fibre bundles and of the spaces between them.

The folds seen in very emaciated persons are likewise caused by the diminution in the size of the rhomboidal spaces. This is brought about by the loss of fat and the consequent change in the arrangement of the fibrous structure of the skin. Coarser furrows are also seen on the palms of the hands and on the soles of the feet, and in these places the skin is not movable. These furrows are always permanent, being caused by the firm union of the skin to the tissues below by means of short bundles

of connective-tissue fibres. Dimples, where they occur, are due to the same cause; that is, the skin is at that point attached to the underlying tissues and does not move together with the rest of the skin of which it forms a portion.

THE STRUCTURE OF THE SKIN.—The integument of the body is composed of several layers. The most external of these consists of epithelium and is termed the epidermis. It clothes the outer surface of the corium, or cutis propria, the line of division between the two being very sharply defined and great morphological difference exists between the elements composing each. The corium is a closely knit tissue, consisting of connective tissue, elastic fibres, and unstriped muscle. It contains the glands of the skin and the hair, and is rich in blood-vessels and in nerves. It is not sharply limited on its under surface, but goes over here gradually into the subcutaneous or fatty layer of the skin. This layer, the panniculus adiposus, is in reality the deeper portion of the cutis, and consists of connective-tissue fibres loosely put together, which contain in their cells and in the spaces between them a more or less large amount of fat.

The epidermis and the corium are the most important portions of the skin, and vary in many particulars on different portions of the body. The various appendages of the skin—the hair, the nails, and the glands—are derived from or are attached to them.

EPIDERMIS.—Embryology.—The epidermis, the most external layer of the skin, is formed from the ectoderm, and in the first month of life and the beginning of the second consists of only a single, or in its thicker portions of two or three rows of polygonal cells. Below these is a layer of very small cells, which represent the origin of the stratum mucosum or rete Malpighii. This increases, in the course of development, to several rows of cells, the layer becoming more and more distinct and thicker. In the mean time the outermost cells have also become flatter, and represent the primitive horny layer, which, however, remains during fetal life of a low grade. It is subjected to constant desquamation, and the scales from its surface are mixed with the secretions from the skin to form the vernix caseosa. As early as the eighth month (Unna), granular cells begin to appear between the horny and mucous layers, and the cornification of the epidermis cells becomes more marked. Nevertheless, and before this, the horny layer has become strong enough to oppose sufficient force to the epithelial growth and to the proliferation of its cells, so that the increase in thickness of the rete Malpighii can no longer take place in the direction of the external surface, but is compelled to proceed downward toward the cutis propria. It penetrates, in its further development, into the spaces between the rudimentary papillæ, springing from the surface of the cutis, and thus forms the interpapillary prolongations of the epidermis. It is by virtue of these ingrowths of the epidermis that, when fully formed, it lies upon the derma as an accurately fitting coat, which follows closely the outlines and inequalities of the true skin.

Thickness of the Epidermis.—The thickness of the epidermis, as a whole, varies from birth to old age, on different parts of the body, and is also influenced by external causes, as pressure, rubbing, etc. At birth it is from 0.15 mm. to 0.25 mm. in thickness, but in adult life from 0.75 mm. to 1.66 mm. The differences are due, for the most part, to the thickness of the horny layer, which in some situations, as on the palms and soles, or on any surface subjected to constant pressure, may attain a very considerable increase in thickness.

Layers of the Epidermis.—The epidermis is divided into two major layers, due to the different consistence of the cells constituting each. The most external and superficial one, consisting of horny cells, is firm and resistant, and termed the stratum corneum, while the one immediately below it, lying in contact with the derma, is called the stratum mucosum, or rete Malpighii. The latter consists of soft epithelial cells and is sharply defined from the stratum corneum. Both of these major layers are still further subdivided according to the ap-

pearance of its cells, or to the reaction of their various portions to certain coloring substances.

Rete Malpighii.—The most deeply situated cells of the stratum mucosum, those which are in immediate contact with the derma, are cylindrical in shape and form the basic layer or stratum basale of the rete. Its importance can be estimated from the fact that it represents the productive part of the stratum mucosum. In normal skin they are the only cells which show the karyokinetic cell figures and indirect division of the nucleus occurring in epithelial growths. Their long axes are directed perpendicularly to the corium, and if the layer is carefully examined, small basic cells, resulting from the cell division, are seen pushing their way in between the older ones.

The cylindrical cells send out into the corium more or less long prolongations, but the spines, which characterize the entire rete, are seen clearly only upon their upper contours. It is in these cells, especially, that a more or less large amount of pigment granules are deposited, which give the various shades of color to the skin of different individuals and races.

Above the basic layer, cells of various shapes and sizes are found. Over the papillæ, and in the interpapillary portions of the rete, round and cuboid and polygonal cells are seen. In the interpapillary prolongations, however, round cells predominate. As the external surface is approached the cells become larger, and have their long axes more parallel to the surface of the skin. The cells themselves have a body consisting of finely granulated protoplasm, which contains a clearly defined nucleus, in which are several nucleoli. According to the position of the cells in the rete, the shape of the nucleus varies. In the uppermost portions it is oval, in the middle, round, and in the cylindrical layer, rod-like, thus agreeing more or less accurately with the shape of the cell. The varying form of all of these cells is due in general to the degree of mechanical pressure to which they are subjected by the individual growth of each, and by other causes, such as atmospheric pressure. The cells composing this portion of the rete Malpighii do not lie in close contact with each other, but are held in apposition by protoplasmic prolongations from their surfaces, which are continuous with the protoplasm of the cell body. They have been termed spines. It is due to this characteristic that the entire layer has been named the stratum spinosum.

The spines, which characterize these epithelial cells, were first observed by Schrön, and the function of binding the cells together has been attributed to them. The manner in which this occurs has, however, always been a subject of controversy. Max Schultze was of the opinion that they were arranged as in a pinion and ratchet; Bizzozero, that their ends were united together; and Ranvier, that their ends were fused together, forming a peculiar elastic organ which allowed considerable movement. These spines can be studied best in rapidly proliferating growths of the rete, as in condylomata acuminata; but in the normal skin it is very difficult to form any opinion in regard to their natural arrangement. Whether the spines are active or passive in their nature is likewise a disputed point. Still, as Unna has pointed out, they are in all probability the result of active protoplasmic movement, since they are purely prolongations of the cell body and consist of the same protoplasm.

Intercellular Spaces.—The arrangement of the spines springing from the surface of the cells of the rete is such that small spaces are left between them. These, the intercellular spaces of the stratum mucosum, are of great importance, inasmuch as they serve as channels for the passage of the nutrient fluids from the corium to the epithelium. The communication existing between the blood and lymph vessels and spaces and these intercellular spaces was clearly demonstrated by Nalepa, who succeeded in injecting them from the subepithelial blood-vessels. The wandering cells coming from the vessels of the cutis and seen in the rete are also enabled to wander

along by means of these spaces, and they are the source of the pigment sometimes seen in these situations.

Stratum Granulosum.—Situated above the stratum spinosum, but yet in close contact with it, is a layer of cells characterized by the possession of certain peculiarities. This layer consists of one or two rows of cells, seldom of more, upon whose surfaces shortened spines may still be seen, and they also contain granules of various sizes and shapes. It is owing to the presence of these that it has received the name of stratum granulosum. These granules react toward certain coloring substances in a marked manner, and stain very deeply. Unna, who has studied this layer very carefully, states that it makes its appearance in the epidermis toward the end of foetal life, but that it can be seen much earlier in the inner root sheath of the embryonic hair.

The stratum granulosum is present over the entire skin, except on the vermilion border of the lips and in the nail bed. The granules appear white by direct light, and for this reason Unna asserts that they are the cause of the white color of the Caucasian race. Such an explanation is, however, scarcely a reasonable one, owing to the fact that this same stratum granulosum is present in the skin of the negro as well as in that of the other dark races; and besides, when it is found pathologically or even under natural conditions greatly increased in depth, it does not seem to cause the color of the portions where it is situated to be whiter than the remainder of the skin. The stratum granulosum is very marked in condylomata acuminata and on the palmar surface of the hands, and yet the former are far from being white in color, and the latter are not especially so.

The granules which are present in these cells have been the subject of so much discussion that they are worthy of extended consideration. They were observed long ago by Kölliker in the medulla of the hair, and by Aufhammer in the epidermis. Langerhans, however, was the first to describe them carefully, while Unna pointed out that they stood in constant relationship to the process of cornification, and he claimed that they represented the intermediate steps which occurred in this process, transforming the soft epithelial cells into horny tissue. Ranvier regarded them as drops of a fluid substance, which existed in a free state in the lowest layers of the stratum corneum, and to which he had given the name of eleidin. Waldeyer, however, has furnished the most satisfactory and correct information in regard to them. He proved that they could not be drops of fluid, because they swelled up on the addition of alkalies and also changed their shape on pressure, but not in the manner that fluids do. They were likewise insoluble in ether, alcohol, or water, and possessed a very great affinity for the nuclei-staining dyes, as hæmatoxylin, picrocarmine, etc. The supposition that they were fatty in character was also excluded by their want of reaction to osmic acid. Waldeyer found, on the other hand, that they agreed chemically very closely with the hyalin of Recklinghausen, a product of degeneration, and for this reason he suggested the name of keratohyalin for the substance.

Keratohyalin, according to Unna, is found to a small extent around the nucleus of the cells in the middle portion of the stratum spinosum, but it exists to a considerable extent only in the stratum granulosum. The granules here are small, and though the cells are filled with them, yet a small peripheral zone always remains free from encroachment. The cells in this layer have atrophied nuclei, which, however, still stain well, and the intercellular spaces are narrowed to such an extent as to be almost entirely absent.

The significance of keratohyalin and its relation to the process of cornification have received much attention. The general opinion at present is in favor of regarding these granules, not as the cause of the cornification of the rete cells, but as a phenomenon accompanying that process, and as one which is produced by the act of cornification taking place in the periphery of the cells.

Stratum Corneum.—The layer of the epidermis lying above the stratum granulosum is the stratum corneum.

It is the one which is most external and is in contact with the air. It varies greatly in thickness on different portions of the body, being, however, usually most marked on the palms of the hands and on the soles of the feet, and also being always much increased on any portion of the skin which is subjected to constant pressure. On these surfaces especially, but not exclusively—that is, on the palms and the soles—it is noticeable that its lowest portion, that which is immediately next to the stratum granulosum, possesses great transparency. This stratum is narrow, sharply defined, and is known as the *stratum lucidum* of Oehl, but its existence has never been satisfactorily explained. The cells forming the stratum corneum are clear and transparent, showing neither granules nor nuclei. Unna claims to have found traces of the spines seen on the cells of the stratum spinosum even here, and asserts that the coherence of the cells forming the horny layer is due to their persistence.

By means of artificial digestion with pepsin and trypsin, it has also been found that the entire cell does not become cornified, but only the peripheral portions. After employment of this method it is clearly seen that it is the contents of the cells which are destroyed, while the peripheral portions remain and have the appearance of horny shells.

The reaction of the epidermis to certain staining materials allows furthermore a recognition of several layers constituting it, and shows successive changes not only in the cell substance, but also in the intercellular spaces. We owe to Unna the following table, showing the reaction of the several layers of the epidermis to various dyes:

Layers of the epidermis.		Consistence.	OSMIC ACID.		Picrocarmine.	Hæmatoxylin (glacial acetic acid).	Iod violet (only slightly decolorized).	Salicylic acid—chloride of iron (H. Hebra).
			Without removal of fatty matter.	After removal of fatty matter.				
A. Stratum corneum	1. Superficial	Firm.....	Black....	Clear....	Yellow	Bluish-white	Blue	Brown. Clear.
	2. Middle	Looser texture	Clear....	Dark brown.	Red	Violet		
	3. Suprabasic	Firm	{ Black ..	{ Clear ..	{ Dark red ...	{ Bluish-white	{ Clear	{ Light brown.
	4a. Basic, stratum lucidum of Oehl.	Very firm						
B. Stratum granulosum .	4b.	Clear....	Dark brown.	{ Yellow	{	{ Blue	{ Not constant.
				
C. Stratum spinosum	Rete Malpighii, stratum of Fleming.	Soft.....	Protoplasm	Granules colored dark red..	Granules colored violet.	{ Nuclei colored blue.	{ Brown.
		Coloring (green).	Nuclei colored dark red.	Nuclei colored blue.		

The several layers which have just been described as entering into the formation of the epidermis should be carefully considered in the study of the anatomy of the skin. It is from the epidermis that the appendages of the skin, the hair, the nails, and the glands, originate and derive their most important parts. We shall refer to this again when describing these various constituent portions of the skin.

THE CORIUM, DERMA, OR CUTIS PROPRIA.—*Embryology.*—The corium, or true skin, is that portion which lies between the epidermis and the subcutaneous or fatty layer. It is derived from a superficial portion of the mesoderm, consisting at first of only round cells. In the second month of fetal life, however, spindle-shaped cells begin to appear, but only very little intercellular substance is present. Very shortly after this, it is noticed that the cells in the upper portion of this primitive corium become more closely aggregated together than in the lower portion, and at the same time the formation of fibrillated tissue begins in this latter. The fibres increase greatly in number, and by the fourth month the presence of fat is detected. It is in this way that the subcutaneous or fatty layer is developed, and it is to be considered, in reality, a part of the derma, since it has the same embryological source, and not a separate and dis-

tinct layer of the skin. The transformations which take place among the closely aggregated cells in the upper portion are shown by the penetration of fibres between them and by the deposition of collagenous material. The individual cells are thereby more and more widely separated from each other, and the corium attains a considerable degree of thickness. Gradually blood-vessels and nerves pass into it, and upon its superficial surface the papillæ begin to form. These latter appear about the sixth month of fetal life as small eminences upon the surface of the cutis. They are formed by the growth of the epidermis, which pushes before it the weaker and more yielding portions of the cutis. They are first seen on the palms of the hands and the soles of the feet, but are quite general toward the end of fetal life. The development of the papillæ is not fully completed until after birth.

Divisions of the Cutis.—The major part of the cutis consists of fibrous connective tissue, which is poor in cells and which is arranged in the form of bundles. The texture of the cutis is closely knit in that portion which is next to the epidermis, but is much looser in the parts below this. In this situation, the fibre bundles crossing each other form the rhombic spaces, which have been mentioned as the cause of the linear cleavage of the skin. On account of the difference in the texture of the cutis, it has been divided into two layers: the one in immediate contact with the epidermis being termed the *pars papillaris*, that below it, the *pars reticularis*.

Pars Reticularis.—The *pars reticularis* of the corium is composed of bundles of fibres of various sizes and lengths. They are continuous with the connective tissue of the

inner portions of the body—the fasciæ, etc.—and pass upward perpendicularly, or slightly inclined to the surface of the skin, until they arrive at the cutis. Here they run obliquely, crossing each other at various angles, and serve as boundaries for spaces which are formed by their intersection. These spaces are, in general, rhomboidal in shape, but oftentimes polygonal, their regularity depending upon the length and uniformity of course of the fibre bundles forming them. The length of the fibre bundles and the absence of their firm adhesion to the underlying tissues are very important factors. It is owing to such an arrangement that the skin is freely movable over the greater portion of the body. On the scalp, the palms of the hands, and the soles of the feet, where these bundles of fibres are short and intimately united to the underlying fascia, the skin is only very slightly movable. These places of intimate union, however, serve as fixed points from which the skin is stretched over the body. The movability of the skin is also limited on the circumscribed portions, where it is in immediate contact with bone, cartilage, or tendons, as over the tibia, etc.

The bundles so frequently mentioned are composed of fibres, which correspond in structure to those of fibrous connective tissue. Under normal conditions they are in

a state of tension, and are for the most part straight, but under the microscope they are found presenting a wavy appearance. Chemical examination has shown that they consist to a great extent of collagenous material. The fibres themselves are bound together in bundles by an albuminous semifluid cementing substance, which Rollet has found to be similar to mucin. According to Fleming, this cementing substance not only exists between the fibres, but also surrounds the bundles, and Tomsa claims that it binds together all the constituents of the cutis.

The fibres possess cells, but they are numerous only in the vicinity of the large blood-vessels. These cells are the usual connective-tissue cells; they are large and contain nuclei and nucleoli. They lie upon the bundles in the same manner as endothelial cells do in the situations where these are found, and for this reason have at times been regarded as forming an endothelial lining for the rhombic spaces between the bundles. It has, however, been demonstrated that they differ from the cells of endothelium in that their edges do not lie in contact with each other, and they do not form a continuous covering for the bundles (Ranvier).

Elastic Tissue.—According to the latest investigations made in regard to the elastic fibres of the skin—a most thorough study of which has been made by Unna—they are exceedingly abundant in the reticular portion of the cutis. By the use of special methods of staining and of preparation, Unna found that, under the form of broad bundles, elastic fibres spring from the fascia below the skin, and, passing up between the fat masses, penetrate into the cutis. In their course they divide continually in a more or less forked manner. These bundles may be traced upward to just below the epidermis. The muscles of the cutis also serve as points of origin for bundles of elastic fibres, and Unna claims that they can be seen attached to the muscles at their points of origin and insertion, having a tendon-like appearance.

Another relatively fixed point of the elastic basework of the cutis is seen in an extensive network of fibres, which follows with the greatest regularity the outline of the epidermis, where this latter is in contact with the corium. This network, which Unna terms the subepithelial elastic net, is situated just below the surface of the cutis, being separated from the epidermis by a narrow homogeneous strip of the derma, in which there are very few blood-vessels. From this network fine fibres are given off, which proceed upward perpendicularly and are lost sight of here and there between two of the basic epithelial cells of the epidermis.

There is, also, in the papillary portion of the skin, an extensive network of elastic fibres. It is formed by the repeated division of fibres which originate from the subepithelial network. All of these elastic fibres do not exist independently of the rest of the cutis, but are more or less closely connected with the fibre bundles of connective tissue which have already been treated of.

The relationship of these elastic networks to the appendages of the skin, such as the hairs and glands, has not yet been thoroughly studied. Still Unna claims that there is some special connection between them and the sweat ducts and glands. The elastic fibres are found to

be entirely absent around the coils, but quite abundant about the ducts, along which they run in a parallel direction. He consequently is of the opinion that the contraction of the elastic network of the skin, acting with the fibre bundles with which it is in close union, produces a pressure on the ducts, and shortens them by

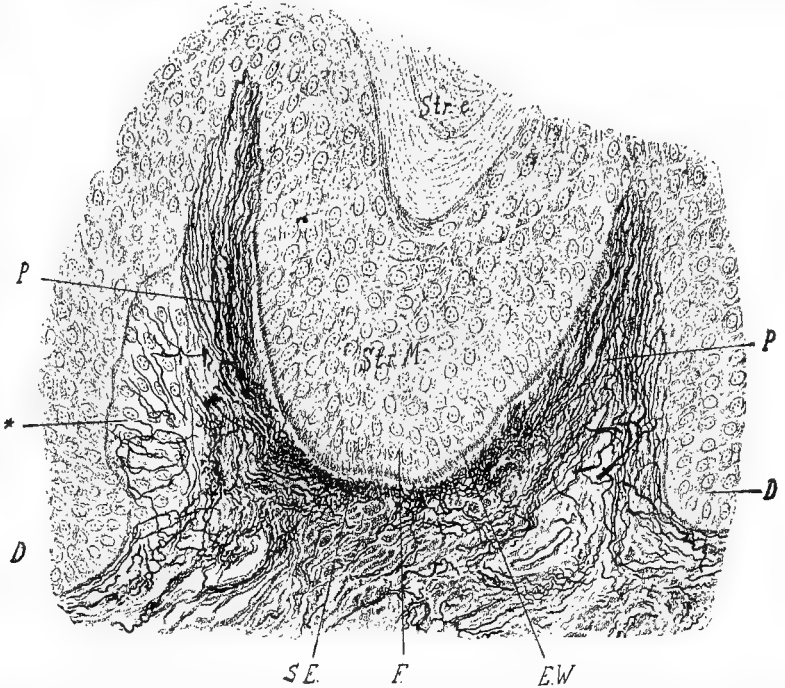


FIG. 5227.—Two Papillæ of the Skin of the End of the Toe. The elastic fibres which they contain have been rendered specially distinct by the use of Weigert's method of staining. This method, while causing the elastic fibres to assume a deep black color, makes all the surrounding tissues appear pale blue. The specimen was hardened in alcohol. P, Papilla; F, fold of the epithelial layer; D, glandular epithelial ridge; Str.M., stratum Malpighii; Str.c., stratum corneum; S.E., subepithelial network of elastic fibres, which are especially abundant around the epithelial fold (F), whereas on the sides of the glandular ridge the network is looser, i.e., it contains decidedly fewer elastic fibres; E.W., basal epithelial cells which are distinguished from the others by their darker coloring.

diminishing the thickness of the skin. In this way the passage of the secretion of the glands through the ducts to the outer surface is favored.

Unstriated Muscle.—With the exception of the palms of the hands and the soles of the feet, the skin of the entire body contains a more or less large number of unstriated muscular fibres and bundles. They are found to attain their highest development in the skin of the scrotum, in the penis, and in the nipple and its areola. The vermicular movements of the scrotum are due to these involuntary muscles, as is also the erection of the nipple. They are situated in the cutis propria, and lie perpendicular to the plane of cleavage of the skin. On the penis they are arranged in a circular manner, and they follow a similar course in the nipple and in its areola.

Besides these, there are other muscles in the cutis which, owing to the connection existing between them and the hairs, are termed the arrectores pili. They are formed by the union of several small muscular bundles, which, originating in the pars papillaris, run an oblique course through the reticular portion of the cutis, and are attached to the hair follicle. The point of their attachment is not uniform—sometimes to the middle portion of the hair sheath, sometimes low down in the lower third. It will usually be observed that in their course to their point of attachment, they curve around the sebaceous gland attached to the hair follicle and are in quite intimate connection with it. According to Tomsa, the fixed point of the arrector muscles is the hair follicle, while the point of movement is the pars papillaris of the cutis.

The arrangement of the involuntary muscular fibres in many places in the derma, as in the cutis of the forehead, cheeks, back, is in the form of a network. This net originates in the pars papillaris and is distributed throughout the upper two-thirds of the pars reticularis. By the action of these muscles the skin is kept more or less in a condition of tension. According to the direction in which they exert their action, the muscles have been divided into horizontal and oblique tensors. The elastic bundles and fibres connected with the muscles play here an important part, inasmuch as Tomsa has shown that they stand in the same relationship to them as do the tendons to the voluntary muscles, and serve as fixed points from which the contraction of the cutis tensors takes place. The action of these muscles also regulates to a great extent the circulation of the lymph in the cutis, while the contraction of the arrectores elevates the hair, compresses the sebaceous glands, and facilitates the propulsion of their secretion into the hair follicle.

The Pars Papillaris Cutis.—The papillary portion of the true skin is constituted by a series of small eminences or papillæ, which spring from its upper or free surface. It is in direct contact with the epidermis, which, as has already been described, sends down prolongations of epithelial cells between the papillæ.

The papillæ of the skin are found most fully developed on the palms of the hands and on the soles of the feet. They are arranged here in long double rows, which form the curvilinear ridges seen in these situations. Between these rows there is a narrow path in which are the external orifices of the sweat ducts. On other portions of the body the papillæ are arranged more or less in groups or in short rows, and the surface of the cutis seems to be divided into rhomboidal spaces of various sizes by the deeper penetration of the interpapillary prolongations of the epidermis. The long diameters of these spaces agree with the line of cleavage of the portion of the skin where they are situated, and their shape is dependent upon the arrangement of the connective-tissue bundles in the reticular portion of the cutis.

The papillæ are more or less conical in shape, sometimes single, or again cleft into two or more points, forming a compound papilla. They differ greatly in shape, size, and distribution on the various portions of the body, and also vary according to the age of the person (Unna), becoming in old age almost flat. They are very numerous on the penis, the nipple, the labia minora, and the clitoris, appearing in these places as low hills. The largest papillæ are found in the cutis of the nipple and of the corona glandis. Those distributed generally over the surface of the body are very small, about 0.05 mm. in height. On the ends of the fingers, under the free borders of the nail, they attain a size of 0.5 mm.; but their height varies in general between 0.05 mm. and 0.2 mm.

The papillary portion of the cutis consists of a closely woven network of fibres, which are derived directly from those forming the pars reticularis. The papillæ are very rich in elastic fibres, and contain blood-vessels, lymphatics, nerves, and, in certain situations, tactile corpuscles. The manner in which the papillary body and the epidermis are joined together must be studied on specimens which have been macerated, and from which the epidermis has been removed *in toto*. When this has been done, it is seen that the entire surface of a papilla has a finely ribbed aspect. On sections made horizontally through them, they look as though their contour was toothed. The ribs have a slightly wavy course and are at times arranged in a concentric manner, having much the same appearance as may be observed on the palmar surfaces of the ends of the fingers. These ribs on the papillæ have been found to correspond to minute furrows on the cells forming the basic or cylindrical epithelial layer of the epidermis and to fit into them, each cell requiring usually three or four ribs. From the fibrillated appearance it might be thought that these ribs were connective-tissue fibres, but such has been found not to be the case. They consist in reality of a transparent homo-

geneous substance, which covers thinly the surface of the papillæ. The proof that it is a distinct membrane has never been satisfactorily made, and it seems better to accept Unna's view, that it stands in intimate connection with the cementing substance of the cutis in general, since it has been found that, when the cutis is subjected to the action of trypsin, this homogeneous substance covering the papillæ disappears in the same way as the cementing substance in other portions of the derma.

THE SUBCUTANEOUS CONNECTIVE TISSUE OR FATTY LAYER.—It was mentioned, in speaking of the embryological origin of the skin as a whole, that the subcutaneous or fatty tissue was derived from the mesoderm. It is that portion which attains its full development the earliest of all the layers of the skin, and in which the deposition of fat between the fibres constituting it takes place very early in foetal life. The subcutaneous connective tissue, or panniculus adiposus, though in reality the lower portion of the corium, is regarded as forming the third layer of the skin, and it is characterized by the presence of a greater or less amount of fat included within its meshes.

It is composed of bundles of connective-tissue fibres, a network of elastic fibres, and of fat, and is very rich in large cells. These have long poles and are situated either in or between the fibre bundles, occurring in the form of spindle-shaped cells. According to Flemming, the masses of fat can be divided into three classes, each of which is characterized by its blood supply; the fat clusters with their own blood-vessels; the strands of fat which lie around the large vessels and receive only a meagre supply of blood from capillaries; and the fat islands which have no blood supply of their own. We have to thank the same investigator for our knowledge of the histology of fatty tissue. He found that the fat cells were derived from ordinary branching connective-tissue cells. They took up fat in small drops, and in proportion as the fat increased in quantity the protoplasm of the cells also increased, and they became round in shape. The protoplasm containing the nucleus is forced to the periphery by the accumulation of fat, and appears as a membrane; but these fat cells have no true enclosing membranes, except when they are old, and when the protoplasm has become thickened into a membrane-like covering. The contents of the cells do not consist of pure fat, but of a mixture of fat and of some product from the protoplasm. At the time of birth the panniculus adiposus is very greatly and uniformly developed over the entire body. As the child grows, however, it diminishes in quantity and remains of considerable extent only on certain portions. Its function is protection to the underlying tissues, and it serves to give roundness to the outline of the body. Those portions of the body which are firmly bound down to the fascia by short bundles of fibres, as the scalp, the skin of the palms and of the soles, etc., possess only a small fatty layer. Where great mobility is necessary, as in the eyelids, or where there is a great amount of muscular tissue, as in the scrotum, the panniculus adiposus is also absent. Over the joints, where the skin lies in close contact with the bones, and by their movements is continually subjected to pressure and tension, bursæ develop in the subcutaneous tissue after birth. In this layer the large arterial and nerve trunks going to the cutis are found, and also the veins and lymphatics which come from the derma and unite to form large efferent branches. In certain localities the Pacinian bodies are also present.

THE GLANDS OF THE SKIN.

There are two sets of glands which are found in the skin, the sweat glands and the sebaceous glands. They differ from each other to a most marked degree, and if considered from the standpoint of their relative importance the former claim priority and more extended study. We shall, therefore, begin with the sweat glands.

THE SWEAT GLANDS.—*Embryology.*—The primary evidences of the development of these glands of the skin

are seen in the fifth month of foetal life. They appear first on the palms and on the soles, under the form of rows of epithelial prolongations from the inferior border of the epidermis into the cutis. At this stage they are

solid, club-shaped, and surrounded by a homogeneous membrane. Their further development consists in the elongation of these epithelial ingrowths downward, and in the formation, by the seventh month, of a cavity along its axis, which is later further extended through the epidermis to the external surface. In the mean time, the gland tube at the end in the cutis has become coiled up, forming a ball, and the excretory duct in its course through the skin is twisted upon itself. The development of these glands is very rapid, and by the end of foetal life they have already attained their full development. In certain situations, however, they enlarge even after birth, and in their structure differ somewhat from the ordinary and smaller ones distributed generally over the body. These larger glands are found in the axillæ, the inguinal regions, around the anus, the nipple, and in the auditory canal (ceruminous glands).

The sweat glands are present everywhere in the integument of the body, with the exception of the glans penis, the under surface of the prepuce, and the vermillion border of the lip. They are small bodies, consisting of a convoluted tube and an efferent duct which leads to the external surface,

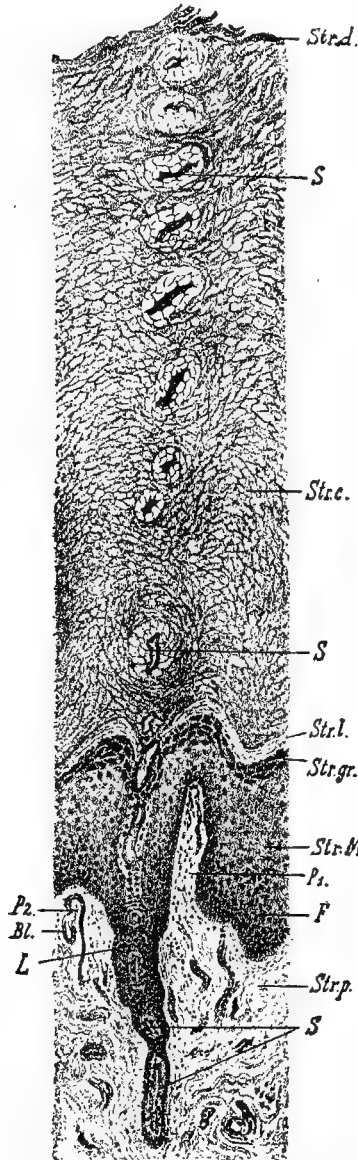


FIG. 5228.—Section of the Skin (epidermis and papillary layer of the corium) of the Sole of the Foot. Specimen hardened in Mueller's fluid; staining with hæmatoxylin and eosin. Magnified 60 diameters. (After Mrazek.) S, Orifice and deeper tubular portion of a sweat gland; Str.d., stratum disjunctum; Str.c., stratum corneum; Str.l., stratum lucidum; Str.gr., stratum granulosum; Str.M., stratum Malpighi; P₁, P₂, papillæ; F, fold of the epidermis; L, glandular portion of the epidermis; Str.p., stratum papillare; Bl., capillary loop in the papilla.

and they are situated in the corium or even in the subcutaneous connective tissue. They vary greatly in size. The coils of the large ones situated in the axilla are from 1 mm. to 2 mm. in diameter; the smaller ones on the general surface are from 0.2 mm. to 0.3 mm. They are most numerous on the palms of the hands,

Krause estimating that there were twenty-eight hundred orifices in a square inch on those surfaces.

The sweat glands, as a whole, are composed of two distinct portions, a secretory and an excretory. The

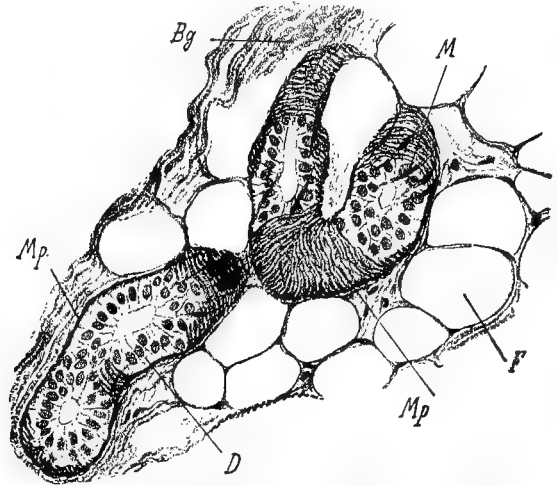


FIG. 5229.—Two Separate Portions of the Secreting Part of the Coil of a Sweat Gland, from the Skin of the Abdomen. Magnified 250 diameters. (After Mrazek.) D, Gland cells; Mp, membrana propria, seen at one point in cross section, at the other as if spread out upon a flat surface; M, muscular fibres; F, flat cells; Bg, connective tissue. The specimen was hardened in alcohol and stained rapidly with orcein.

former is represented by the coils, the latter by the duct which leads to the external surface of the skin. The histological anatomy of the smaller glands differs somewhat from that of the larger ones, and will be considered first.

Histological Anatomy.—The coils, or secretory portions of the sweat glands, consist of a single layer of columnar epithelium, arranged around a rather irregularly shaped lumen. The cells are cloudy throughout, with the exception of a narrow portion along their free margin, which is clear. They are bounded externally by a layer of involuntary muscular fibres, which run spirally around the mass of cells, and which are so arranged that small spaces are left between them. The secreting cells send out processes into those spaces, and these form a union with the limiting membrane or membrana propria of the glands, which is composed of connective tissue. The excretory portion of the gland, or duct, consists of a connective-tissue coat, a structureless membrane, and bounding its lumen are two rows of epithelial cells, the free margins of which are covered by a cuticula. There are no muscle fibres in the coats of the sweat ducts. These latter begin in the inner portion of the coils, and rise to the surface in an oblique direction having a more or less spiral course, and they always reach the epidermis at an interpapillary prolon-

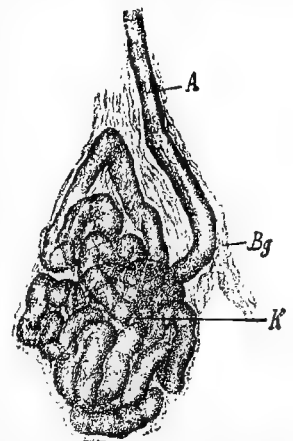


FIG. 5230.—Terminal Coil of a Sweat Gland, from the Skin of the Back of the Foot. Obtained by Professor Schaffer as a separate and complete specimen by maceration in diluted nitric acid. Magnified 80 diameters. (After Mrazek.) K, Terminal coil; Bg, enveloping connective tissue; A, outlet of the gland.

gation. The duct here loses its membrana externa, which goes over into the tissue of the papilla, and also its cuticula, so that the lumen is bounded for a short distance in the stratum spinosum by the spiny cells

as has been already mentioned, differs somewhat from that of those just described. The differences are shown both in the coils and in the duct, by a dilatation and a narrowing of the canal in places. Where the lumen is larger there is only a single layer of epithelial cells; but in the narrower portions there are several. It is also claimed that muscle fibres are present in the former situations, but they are always absent from the latter.

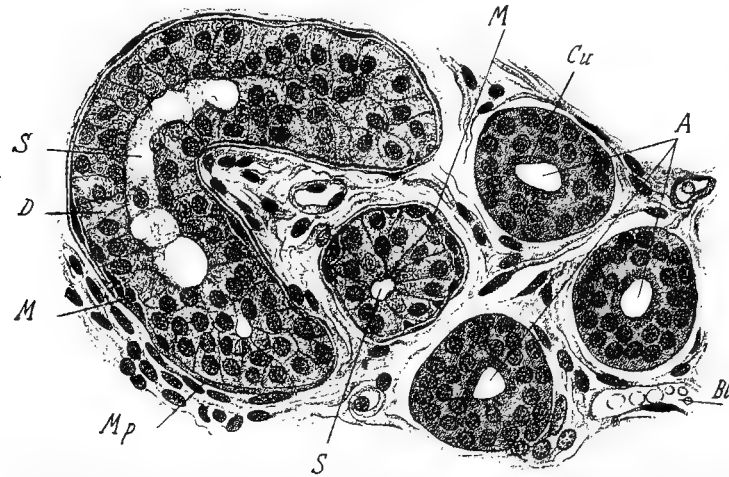


FIG. 5231.—Portion of a Sweat Gland from the Skin of the Back of the Foot. Magnified 400 diameters. (After Rabl.) S, Secreting portion of the coil; D, gland cells; M, smooth muscle fibres; Mp, membrana propria of the glandular tube; A, cross sections of the outlet portion of the gland; Cu, cuticula of the same; Bl, blood-vessel. Specimen hardened in a saturated aqueous solution of bichloride of mercury, and stained with hæmatoxylin and eosin.

alone. The cells which limit the lumen in its course through the epidermis, show granules of keratohyalin very early, and considerably below the level of the stratum granulosum; and it can further be seen that all the layers of the epidermis became interested and aid in forming the boundaries of this spiral canal in its course to the external surface. The views which are held by Unna, in regard to this portion of the duct, have so much in their favor as to claim general recognition. He does not consider that the spiral portion in the epidermis belongs entirely and alone to the duct of the sweat gland, of which it seems to be a continuation, but thinks that it is a canal which is also in connection with the system which conveys the juices throughout the epidermis. According to him, the sweat duct ends in the basic layer of the stratum spinosum, and he would, consequently, separate the two portions very sharply. He very rightly points out, in support of this, that we have no reason for concluding that the fluid which passes through it comes entirely from the same source, inasmuch as there are no grounds for asserting that the sweat is derived from the coils alone.

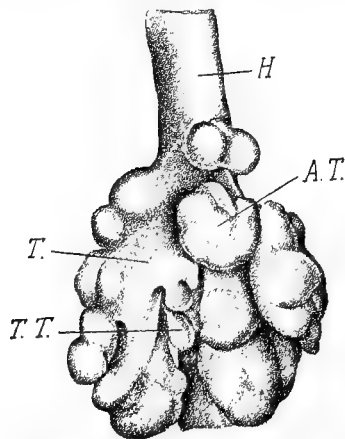


FIG. 5232. Model of a Group of Sebaceous Glands Surrounding a Hair of the Scalp. (After Rabl, from K. Bauer.) H, Hair follicle; T, sebaceous gland; T.T., tubular gland; A.T., alveolar gland.

All that we do know is, that it appears upon the external surface at the openings of these canals, but more than that has not been proved.

The histological anatomy of the larger sweat glands,

tion of the rete into the cutis.

Distribution and Size.—The sebaceous glands are distributed very generally over the body, and are found everywhere in the skin, except upon the palms of the

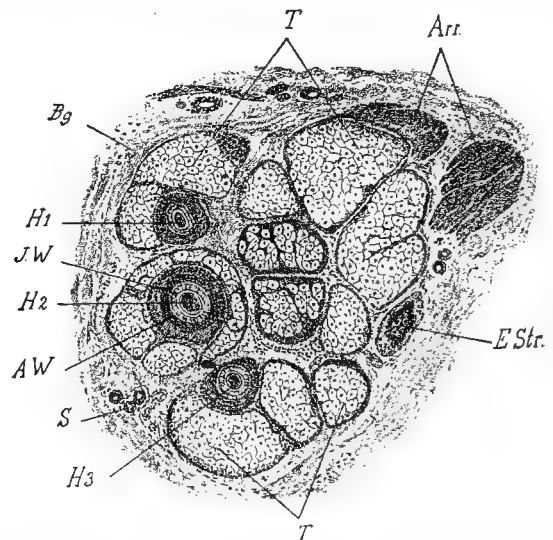


FIG. 5233.—Cross Section of a Hair and Neighboring Parts at the Level of the Sebaceous Glands. The specimen, which had been taken from the scalp of an adult, was first hardened in Mueller's fluid and then stained with hæmatoxylin and eosin. Magnified 50 diameters. (After Rabl.) H₁, H₂, H₃, Cross sections of three hairs; E.Str., a column of epithelial cells, constituting the connecting link between those which surround the hair bulbs (belonging to the hairs shown in the picture) and those lying above the papilla of a fourth hair; T, sebaceous glands belonging to the hairs shown in the cut; J.W., inner root sheath; A.W., outer root sheath; Arr., arrector pili; Bg, connective tissue; S, sweat gland.

hands, the soles of the feet, and the last phalanges of the fingers and of the toes. They are particularly numerous upon the face and the scalp, where they are set very closely together. On the rest of the body they are found

to be fewer in number and more widely separated. The glands vary very greatly in size. Of those connected with the hairs, the smallest are the ones on the scalp, 0.1 mm. to 0.16 mm. in diameter, but larger ones are attached to the hairs of the beard and axilla, from 0.16 mm. to 0.24 mm.; but the largest are on the mons veneris, the labia majora, and the scrotum. The sebaceous glands which are in connection with the lanugo hairs are from 0.25 mm. to 1 mm. in diameter. The length of the glands is from 40 to 160 μ , but the large ones on the nose measure even as much as 1 mm.

In shape there is also considerable variation. The simplest ones resemble small pouches, but the glands are usually found to be racemose or acinous, that is, composed of several lobules which possess one duct in common.

These glandular bodies are situated for the most part in the upper portion of the corium, above the level of the coils of the sweat glands. Some extend, however, through almost the entire thickness of the cutis.

They are found either directly attached to the hair follicles, into which their ducts open, at a variable distance from the orifice on the cutaneous surface, and empty the fatty matter secreted by them; or the external opening of their ducts is situated on the surface of the skin. These latter are the glands with which the lanugo hairs are associated. Besides these two forms, there are others which are entirely unconnected with hairs, and which also open directly upon the outer surface of the skin.

The sebaceous glands which open into the cavity of the hair follicles are the most numerous. They are seen wherever fully developed hairs exist, as on the scalp, the beard, etc. There is sometimes only one gland, but more often there are two, situated on opposite sides of the follicles, of different sizes, and at different heights. Their excretory ducts are short and pass obliquely upward to enter the follicles, the larger glands opening more superficially, the smaller ones more deeply, but the common location is at the junction of the upper and middle thirds.

The sebaceous glands which are associated with the lanugo hairs, and which open directly upon the external surface, are distributed over the forehead, cheeks, sides of the nose, and areola especially. They occur also more or less scattered over the trunk, the extremities, and the genitals. These glands are the largest, and also the most complicated in their structure. The duct is usually broad, and its orifice dilated. The hair attached to it is really an appendage, and passes through the duct to reach the outer surface of the skin. It has no follicle of its own, except at its deepest portion.

The glands which are in no way associated with hairs, and which open directly upon the external surface, are certain ones situated in special localities. They have received distinguishing names, and are known as the Meibomian glands in the eyelids, and the glands of Tyson on the glans penis and prepuce. To this class also belong the large glands of the labia minora, and those of the vermilion border of the lip.

Histological Anatomy.—A sebaceous gland may be considered to be composed of an outer wall and an inner mass of cells. The wall is formed of connective tissue, which is derived from the external sheath of the hair follicles; but in those glands which are associated with the rudimentary or lanugo hairs, and in those unconnected in any way with hairs, the fibrous envelope is obtained from the corium. The wall acts as a support (Morel) for a base-

ment or membrana propria, which bears upon its inner surface a layer of cylindrical epithelial cells, and it also contains the nerves, blood-vessels, and lymphatics supplied to the glands. The membrana propria is exceed-

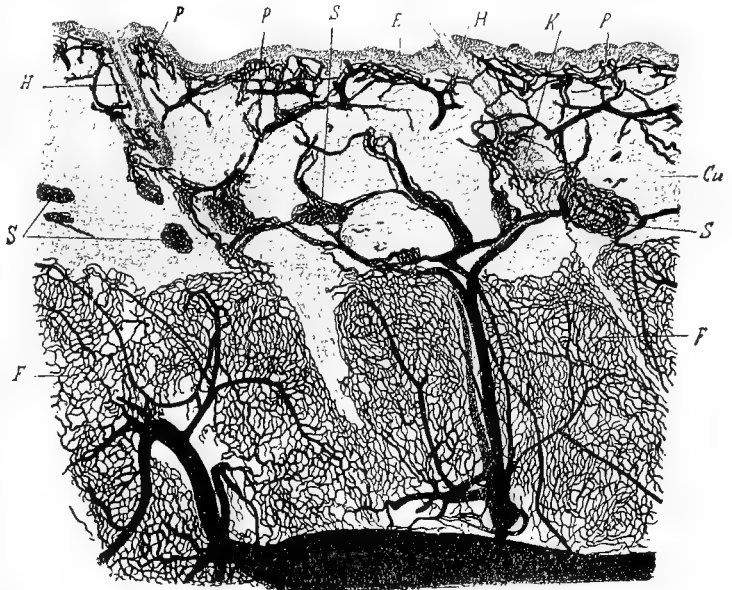


FIG. 5234.—Section of the Skin of the Shoulder of a Child. The blood-vessels have been completely filled with gelatin colored with carmine. Magnified 40 diameters. (After Rabl.) E, Epidermis; P, papillæ; Cu, corium; F, subcutaneous fat tissue; H, shaft of hair; K, bulb of hair; S, coil of sweat gland. The specimen therefore shows, besides the larger trunks of blood-vessels, the capillaries belonging to the papillary layer, the sweat glands, parts of blood-vessels that supply the hairs and also those vessels which belong to the fat tissue. The large trunk of a blood-vessel seen at the lower margin of the picture is situated in the horizontal plane of connective tissue which serves to separate the subcutaneous fat tissue into two superposed layers. In the picture only the upper half of the panniculus adiposus is visible.

ingly thin and amorphous. The single row of cells which are in connection with it is a continuation of the basic layer of the epidermis, the spiny cells stopping at the neck of the glands. The cavity of the glands is filled with large oval and polyhedral cells having large nuclei, but in the central portions there is a semifluid homogeneous mass, the sebum. The source of the sebum seen in the sebaceous glands are the cells, which are found presenting all stages of fatty degeneration. The most external ones are granular, the succeeding ones contain small drops of fat, which gradually increase in size as the central portion of the cavity is reached, until there is no trace of protoplasm remaining, the cell being completely filled with fat.

THE BLOOD-VESSELS OF THE SKIN.—The vessels which supply the skin with blood are branches from the larger arteries which lie below the subcutaneous fatty tissue. They pass up through this latter and form at its junction with the corium a more or less horizontal network. From this network further branches are given off, some to supply certain portions of the skin, others to ascend obliquely and perpendicularly through the cutis, having only few branches, until they reach the subpapillary layer of the corium. Here they again form a more or less horizontal network, which also gives off many branches.

The plexus of arteries at the junction of the cutis and subcutaneous tissue is very rich. It supplies the papillæ of the hair, the coils of the sweat glands, and also sends off branches which break up into capillaries in the panniculus adiposus. The subpapillary network of arteries supplies vessels to the external root sheath of the hair, the sebaceous glands, the unstriped muscles, and the ducts of the sweat glands. In addition, this plexus gives off branches which break up into capillaries just

below the papillæ, and into each of these a tortuous arterial capillary ascends almost to its upper end, where it forms a loop and goes over into a venous capillary. These latter unite to form venules in the same plane as

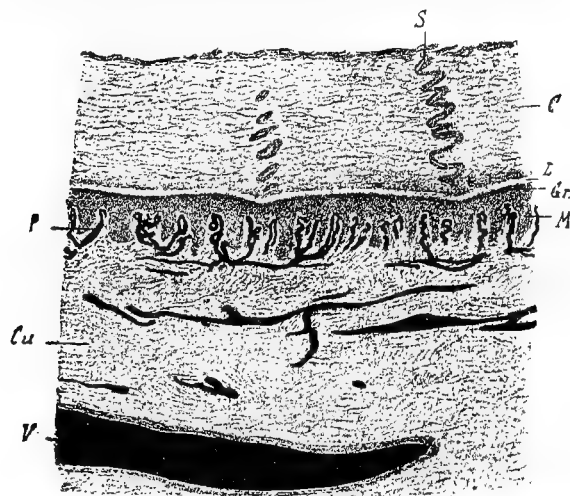


FIG. 5235.—Section of the Skin of the Palm of the Hand. The cutting was done in a direction parallel to the ridges. The blood-vessels have been filled with gelatin colored by carmine. Magnified 50 diameters. (After Rabi.) C. Stratum corneum; L. stratum lucidum; Gr. stratum granulosum; M. stratum Malpighii; P. papillæ; Cu. corium; V. vein at the lower border of the corium; S. orifice of a sweat gland. Portions of the cutaneous plexus of blood-vessels and of the capillaries belonging to the papillæ are also shown in the picture.

the arteries, and course along them. When they arrive at the subcutaneous layer they, together with the veins from the other portions of the cutis, unite to form large venous trunks in the same plane as the large arteries. Between the two horizontal plexuses of arteries there

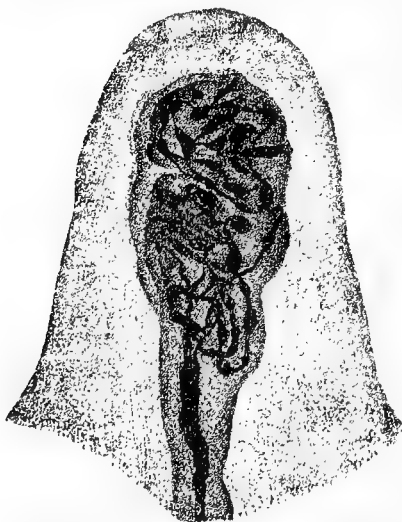


FIG. 5236.—Meissner's Tactile Corpuscle in a Papilla of the Tip of the Finger. The nerves have been stained by Fischer's gold method. (After Rabi, from Ruffini.) An afferent medullated nerve fibre enters the corpuscle from below and subdivides into a number of non-medullated varicose fibrillæ which traverse the corpuscle chiefly in a horizontal direction.

is a portion of the cutis which has a very poor blood supply, and here even the bundles of fibres which go to form the pars reticularis do not receive any vessels.

There are considerable differences in the distribution of the blood-vessels of the skin, and in the area supplied by any one branch. These areas are very small on the palms of the hands, the soles of the feet, and the face; also at the sulcus coronarius and

branch are much larger in the greater part of the skin—the vessels breaking up into a number of capillaries—

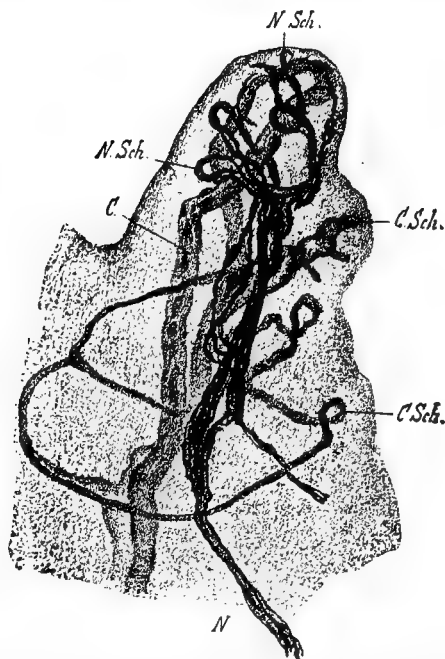


FIG. 5237.—Papilla from the Skin of the Tip of the Finger, showing Capillary Blood-vessels and Numerous Nerve Fibrillæ. Gold preparation. (From Rabi, after Ruffini.) N. Nerve trunk; C.Sch., capillary loop; N.Sch., nerve filaments surrounding the capillaries. (Greatly enlarged.)

and it is in general observed that they are more extensive on the extensor than on the flexor surfaces of the extremities.

Peculiar circulatory conditions are found in certain portions of the skin. On the ear, the alæ nasi, and in the region of the lips, large lacunæ are seen into which the venous capillaries empty from above, while from below the venules are given off. On the ends of the fingers there is likewise a special arrangement of the vessels. It has been found that here some branches of the digital arteries emptied directly into the large veins of the bed of the nails, without there being any intervening capillaries. Also it is observed that, after the vessels for the panniculus adiposus and sweat glands had been given off, but before the upper horizontal plexus for the supply of the papillæ

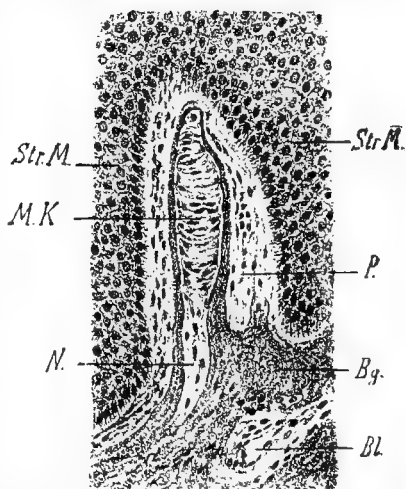


FIG. 5238.—Meissner's Tactile Corpuscle from the Skin of the Tip of an Adult Finger. Specimen hardened in alcohol and stained by means of hamatoxylin and picrofuchsin. (After Rabi.) MK, Meissner's tactile corpuscle; N., afferent nerve fibre; P. papilla; Str.M., stratum Malpighii; Bg., connective tissue of the body of the papilla; Bl, blood-vessel.

the upper horizontal plexus for the supply of the papillæ

had been formed, small arterial branches divided and broke up into many small coils. In the inner portion of these they emptied directly into venules.

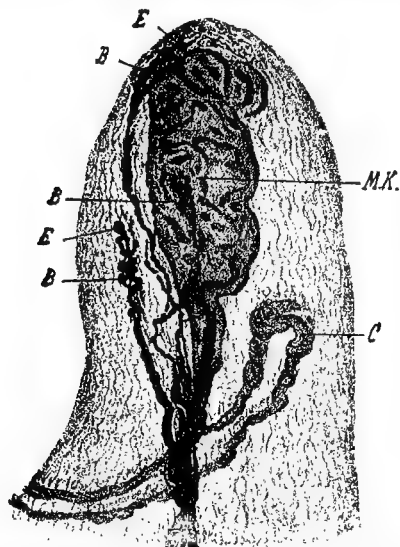


FIG. 5239.—Papilla of the Skin of the Finger. Staining by Fischer's gold method. (After Rabl, from Ruffini.) The papilla contains, at its extremity, a Meissner's tactile corpuscle (MK); farther down, a capillary loop (C), and on the left three independent, fascicular terminal plexuses of nerve fibrillæ (B); E, small terminal knobs of the nerve fibrillæ.

The lumen of the arteries of the skin is narrow, but that of the veins is large and wide. Their coats are slightly marked in the cutis, and they show only near the subcutaneous connective tissue an adventitia and a media. But even there these are poorly developed. All the vessels of the papillary layer of the corium are capillary in character, that is, simple endothelial tubes.

THE LYMPHATICS.—There are in the integument of the body two forms of channels which contain the lymphatic fluid, and through which it flows, viz., the lymphatic vessels proper, those which possess an endothelial lining, and the numerous spaces which occur between the elements composing the various layers of the skin.

In regard to the latter, it has been proved that they are the origin of the lymphatic system of the skin, by the successful injection of the intercellular spaces in the spiny layer of the rete Malpighii from the lymphatics of the subcutaneous connective tissue (Retzius, Axel Key, et alii). Other lymph spaces exist between the membrana propria and the secreting cells of the coils of the sweat glands, and between the epithelial cells of the sweat ducts. The intercellular spaces in the stratum spinosum of the hair follicles and in the sebaceous glands are also points of origin for the lymphatics. The bundles of unstriped muscle fibres and the coils of the sweat glands and the bundles of connective-tissue fibres forming the cutis are sheathed by lymph spaces, as are also the fat clusters. According to Klein, very fine channels proceeding from these lymph sheaths penetrate into the latter and ramify between all the fat cells of which they are composed.

The papillæ are also extensively traversed by lymph spaces, which empty into the lymphatic vessels proper. These vessels are lined with

and at its junction with the subcutaneous connective tissue unite to form a few large vessels, which, according to Heming, have a muscular coat.

THE NERVES OF THE SKIN.—The nerves which are supplied to the skin are derived from branches of the cerebro-spinal system. They pass up through the subcutaneous connective tissue, in the same manner as the blood-vessels, from the larger trunks situated below. In the upper part of the panniculus adiposus the course of the nerves is a horizontal one, and they give off a large number of small branches for its innervation. They penetrate the cutis together with the arterial vessels, and accompany them more or less in their distribution. In their course they give off branches to supply the various constituent portions of the cutis. Those which supply the hair follicles pass to them in the neighborhood of the sebaceous glands, to which fibres are sent. They penetrate the hair sheath and are distributed between the cells of the root sheaths. The sweat glands

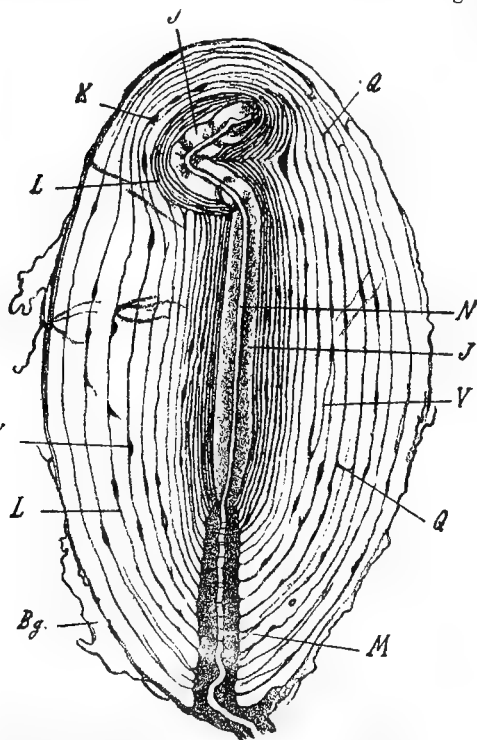


FIG. 5241.—Pacinian Corpuscle from an Amputated Foot. Magnified 70 diameters. (After Rabl, from Henle and Kölliker.) M, Medullated nerve fibre; N, non-medullated nerve fibre within the inner club-shaped sheath; J, L, lamellæ of the outer bulb-shaped envelope; K, nuclei of the connective-tissue cells; V, spot where two contiguous lamellæ unite, the lines of union forming an acute angle; Q, spot where the line of union runs transversely; Bg, connective tissue outside the corpuscle.

and their ducts are also furnished with nerves. Unna claims to have seen nerve endings between the secretory epithelial cells of the coils.

When the nerves arrive at the upper portion of the cutis they take a horizontal course and form a rich plexus just below the epidermis, which gives off a great number of branches. These break up into fine fibrillæ, and are distributed in every direction. These fibrillæ terminate either in the endothelium of the papillary blood-vessels, or free in the connective tissue of the papillary body, or penetrate into the interepithelial spaces of the stratum spinosum. Longer branches from this plexus ascend into the papillæ, and in certain portions of the integument end in the tactile corpuscles.

The nerve fibres which, it is claimed, have been traced between the cells of the epidermis are non-medullated.

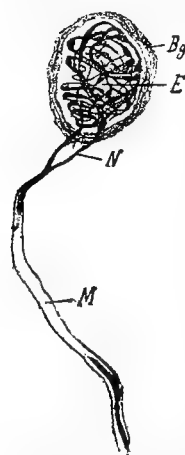


FIG. 5240.—Krause's Terminal Bulb from the Palpebral Conjunctiva. Nerves stained by means of methylene blue. (After Rabl, from Dogiel.) M, Afferent medullated nerve fibre; N, one of the non-medullated nerve fibrillæ resulting from the subdivision of the fibre M; E, terminal coil; Bg, connective-tissue capsule.

endothelium, and begin in the upper third of the papilla (the Hoggans) by means of a cul-de-sac. They course downward in the form of a plexus through the cutis,

They are said to be distributed generally throughout the rete Malpighii, as far up as the stratum granulosum, and to end in the intercellular spaces, either tapering to a

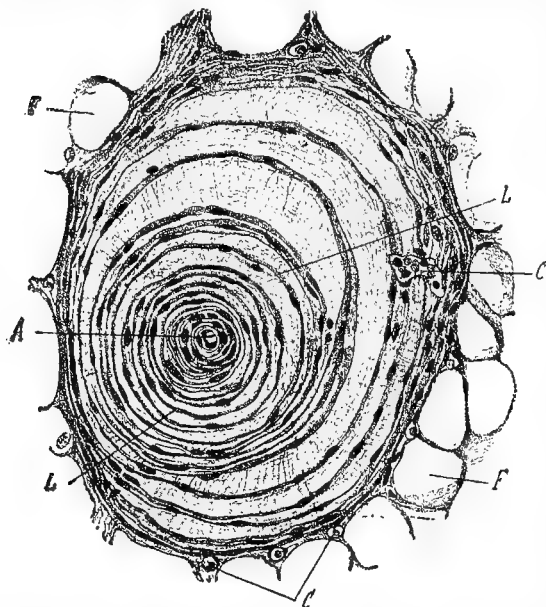


FIG. 5242. Transverse Section of a Pacinian Corpuscle, from the Skin in the Neighborhood of the Anus. Specimen hardened in a solution of picric and bichloride of mercury and stained with hæmatoxylin and eosin. Magnified 200 diameters. (After Rabl.) A, Axis cylinder lying in a narrow, circular, perfectly clear space, the inner club-shaped sheath; L, lamellæ of the outer capsule or envelope; C, capillaries; F, fat cells.

point or with a small rounded extremity. Unna claimed that they terminated in small discs upon the cells, but his view has not received recognition.

Besides the above-mentioned ways in which the nerves end in the skin, there are special forms of termination. These are represented by the tactile corpuscles, the tactile discs of Ranvier, the Pacinian bodies, and the end bulbs of Krause.

Tactile Corpuscles.—The tactile corpuscles are very small, oblong bodies from 40 to 200 μ in length, and from 30 to 60 μ in breadth. They are situated in the upper portion of a broad papilla, and are found especially on the fingers and toes, and in the palm of the hand. They have a distinctly striated appearance, and are directly connected with one or two medullated nerve fibres which wind around the corpuscle, and, on entering it, lose their medullary sheath, the perineurium becoming continuous with the capsule of the corpuscle. The nerves split up into branches, which end in flattened knobs between the connective-tissue cells of which the corpuscle is composed. They often consist of two or three sections lying close together, each one being supplied with a nerve.

Ranvier's Tactile Discs.—These discs are small cup-shaped bodies, the concave side of which is always directed toward the free surface of the epidermis. At several points on the convexity of the disc the termination of a non-medullated nerve fibre is seen. Ranvier claims that this nerve ends only on the surface of these discs, but according to others this takes place in the cell between the nucleus and the external membrane. This form of nerve ending has been found in the deeper portions of the epidermis, near the sweat duct, and in the corium just below the rete.

The Pacinian Bodies.—The Pacinian bodies were first thoroughly described by Pacini, though they had already been mentioned by Vater over a hundred years ago. They are small, oval, transparent bodies from 2 to 3 mm. long and 1 to 2 mm. broad, and are situated in the subcutaneous connective tissue, almost exclusively upon

the branches of the nerves which supply the skin of the palms of the hands and of the soles of the feet, but also upon the dorsal nerve of the penis and of the clitoris. They are likewise found in other places, as around the joints, where they are deeply situated, and also in the mesentery, etc. The major part of the Pacinian body is formed by the capsule. This capsule is derived from the perineurium of the nerve, which ends in the corpuscle, and is in reality composed of a large number of concentrically arranged laminae, which are separated one from the other by a layer of flat endothelial cells. Between any two of these there is a more or less large quantity of an albuminous fluid, and connective-tissue fibres forming septa are also seen. This laminated and concentrically arranged capsule surrounds a narrow cylindrical space, which contains a granular substance in which a few cells are seen, and the termination of the nerve fibre. At its entrance into the cavity of the Pacinian body, the nerve loses its medullated character and the axis cylinder alone passes in. It appears as a pale, finely granular, narrow band, which ends in a single small knob or in a series of them. The nerve has also been observed to pass entirely through one of these bodies and end in another. A small artery penetrates the capsule of the Pacinian bodies along with the nerve, and forms a capillary plexus between the peripheral laminae.

End Bulbs of Krause.—The end bulbs of Krause are minute oval or cylindrical bodies, which are regarded as being more or less related to the tactile corpuscles. They consist of a connective-tissue capsule containing a large number of cells which form a core. Between these, one or more nerve fibres end. They are found in the conjunctiva and the mucous membranes of the mouth, the glans penis, clitoris, and vagina, where they are termed genital corpuscles. The capsule of these end bulbs is derived from the perineurium, but the nature of the core which it contains is still a mooted point. The axis cylinder alone penetrates into this core, having lost its medulla, and it ends in the upper portions either free or as a small button-like protuberance.

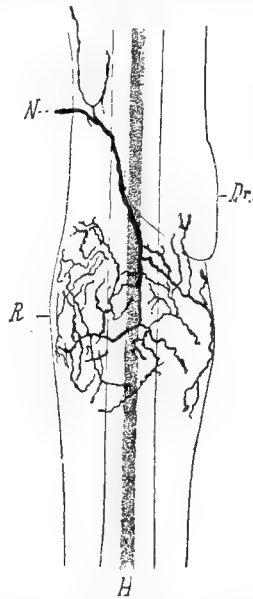


FIG. 5243.—Hair from the Lip of a Human Embryo 19.5 cm. long. (After Rabl, from G. Retzius.) N, Afferent nerve fibre, which first gives off a small forked branch in an upward direction, and then subdivides into a ring-like plexus (R) completely surrounding the outer sheath of the hair root which at this point is somewhat thickened. This plexus consists of a few nearly horizontal fibrillæ between which run numerous vertical ones; Dr, sebaceous gland.

THE APPENDAGES OF THE SKIN.

THE NAILS.—*Embryology.*—The first steps in the development of the nails occur in the third month of fetal life, and consist in the marking out of the nail bed and furrow. This is covered by the ordinary stratum corneum of that period of life, and it represents the eponychium of Unna. Underneath the eponychium the embryonic nail remains up to the fifth month. According to Kölliker, there appears in the fourth month, between the eponychium and the stratum mucosum, a layer of large, pale-colored, horny plates, which cover the bed of the nail and represent its primary form. The nail in its further growth increases in thickness quite rapidly, possesses a free border by the sixth month, and by the seventh month is fully formed. Kölliker also claims that the development of the nail takes place from

the entire nail bed, but Unna insists that he has observed the formation of a germinal spot in the matrix, from which the embryonic nail grows and pushes itself forward beneath the eponychium.

General Characteristics.—The nails of human beings are elastic structures of a horny texture situated upon

portant part, and it is from this portion that regeneration of the nail is continually going on.

THE HAIRS.—Embryology.—The first steps in the development of the hairs occur at the end of the third or the beginning of the fourth month of fetal life. They are shown by the formation of small, solid prolongations of

the rete Malpighii, penetrating into the cutis and increasing in length by the proliferation of the cells composing them. Arriving in the deeper portion of the cutis, the lower end of the prolongations is very soon surrounded by an aggregation of round and spindle cells, which partly form the papilla of the hair and partly grow around the epithelial ingrowth in order to form the sheath of the hair follicle (Unna). During this time changes also take place in the epithelial column. In its inner portion a conical-shaped mass of cells, with its apex directed externally, becomes differentiated from the remainder, and this represents the primitive hair body. From it the hair and its inner root sheath are formed. The primitive hair body having grown around the newly formed papilla, it increases in length upward and keratification begins and proceeds from above downward. The external root sheath is constituted by the portions of the epithelial ingrowth of the rete Malpighii which remain after the differentiation of the primitive hair body and surround the entire hair.

From the sixth to the eighth month of life the foetus has become covered with hair, which, however, falls out

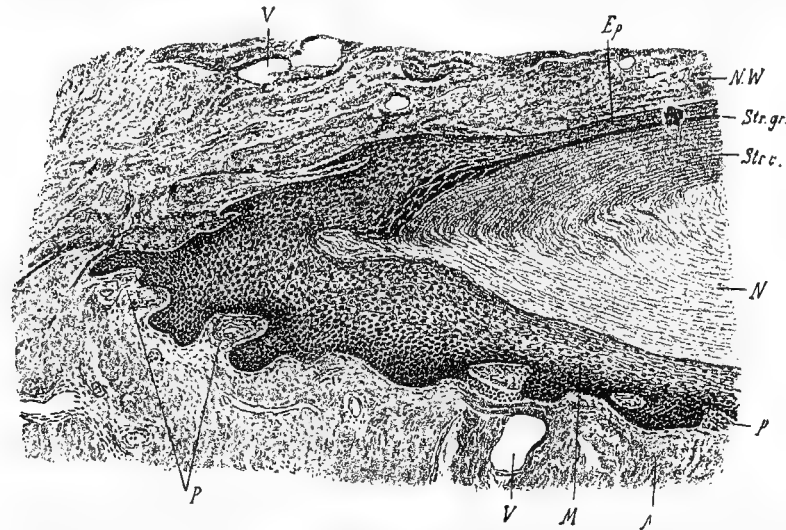


FIG. 5244.—Longitudinal Section of the Bed of the Nail, with the Posterior End of the Root of the Nail. The entire specimen was dissected free from the bone (last joint of toe.) Alcohol was used for hardening the tissues and hæmatoxylin and picrofuchsin for coloring them. Magnified 80 diameters. (After Rabl.) *N.W.*, Wall of the nail; *Ep.*, eponychium; *Str.gr.*, stratum granulosum; *Str.c.*, stratum corneum, colored a reddish-yellow by means of picrofuchsin; *N.*, nail, colored yellow; *M.*, matrix of the nail; *P.*, papilla; *V.*, vein of the corium beneath the matrix.

the dorsum of the last phalanges of the fingers and of the toes. Each one is convex upon its external surface, concave upon its internal and moulded upon the cutis, to which it is firmly adherent. The exposed portion of the nail is called its body; the anterior extremity, the free edge; the semilunar portion posteriorly, which is of a white opaque color, the lunula. The portion of the cutis upon which the nail is situated is the nail bed. It is bounded laterally by two rolls of the skin, which are known as the walls of the nail. Around the nail bed is a groove which is covered by the nail wall, and in this lie the lateral edges of the nail, while the posterior portion, the nail root, is implanted in a similar though much deeper groove; this latter represents the matrix, and it is from here that the growth of the nail takes place.

Histological Anatomy.—The bed of the nail consists of the corium and the stratum mucosum. The connective-tissue bundles of the cutis run here partly longitudinally and parallel to the axis of the fingers, partly in a perpendicular direction from the periosteum to the external surface. The epithelium covering the corium is composed of cells identical with those in the stratum mucosum of the epidermis, and is sharply defined from the nail, except at the matrix.

The corium at the matrix of the nail shows a well-developed papillary body, and is very vascular, each papilla receiving a blood-vessel. In front of this and beneath the lunula the papillae are very small, and still more so anteriorly; the cutis forming the nail bed has no papillae but fine longitudinal ridges, in which run the blood-vessels, which give off capillary branches at regular intervals. These ridges of the corium are covered by the epithelial cells of the stratum mucosum, which also dips down between them.

The nail itself consists of horny lamellae, which are closely bound together, and which are composed of cells similar to those of the epidermis, except that they contain nuclei.

In the formation of the nail the matrix plays the im-

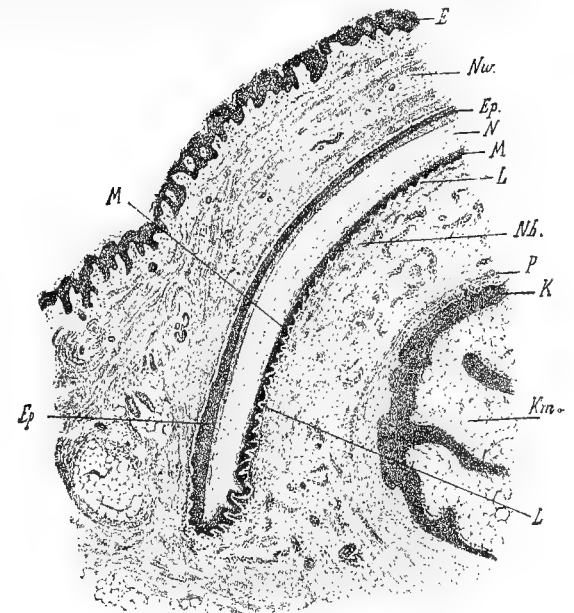


FIG. 5245.—Cross Section of the Basal Portion of the Nail of an Adult. Specimen hardened in Mueller's fluid and stained with hæmatoxylin and eosin. (After Rabl.) *E.*, Epidermis of the wall of the nail (*N.W.*); *Ep.*, eponychium; *N.*, nail; *M.*, matrix of the nail; *L.*, longitudinal border of the matrix; *Nb.*, bed of the nail; *P.*, periosteum; *K.*, bone; *Km.*, bone marrow.

and is replaced by new hair. This regeneration of the hair on the foetus is continuous as in adults, but the

rapidity of the change ceases a few weeks after birth. The embryonic or lanugo hairs, which have a much shorter length of life than those which grow after birth, give place to more permanent ones, and on certain por-

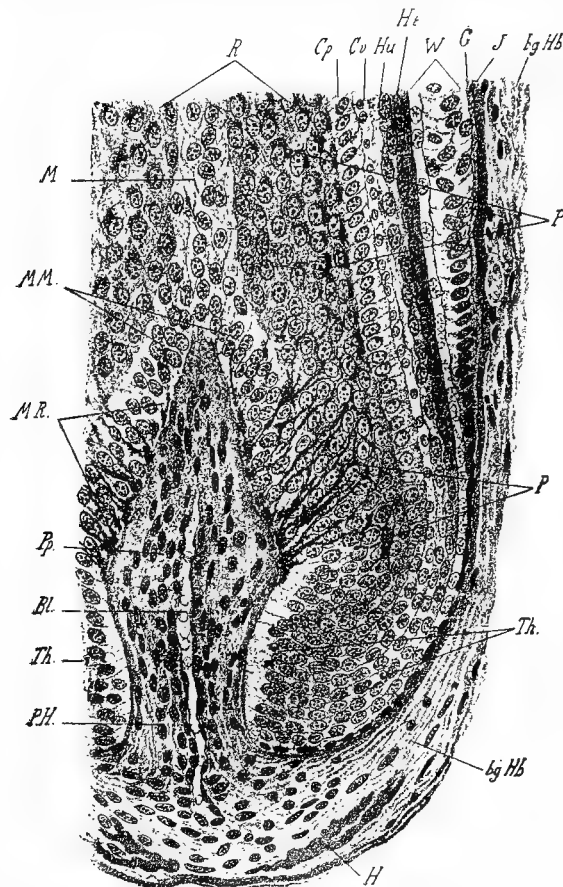


FIG. 5246.—Longitudinal Section of a Papilla, a Hair Bulb, and the Lowest Part of the Shaft of the Hair with its Sheaths, from the Scalp of an Adult. Magnified 300 diameters. (After Rabl.) *Pp.*, Papilla; *P.H.*, neck of the papilla; *BL.*, blood-vessel; *M.*, cells of the medulla of the hair; *R.*, cortical cells; *MM.*, matrix cells of the medulla; *MR.*, matrix cells of the cortex; *Th.*, cells undergoing karyokinesis; *P.*, pigment; *Cp.*, membranous envelope of the hair; *Cv.*, membranous envelope of the root sheath; *Hu.*, Huxley's layer; *W.*, outer root sheath; *G.*, vitreous membrane; *J.*, innermost layers of the connective-tissue hair follicle (*kg HB.*); *H.*, kollastin.

tions of the body acquire a much greater development than they do on others. The new hairs originate from the epithelium forming the external root sheath of the lanugo hairs, which sends out solid buds from which the hair develops in exactly the same way as has just been described, and grows up alongside of the embryonic hair to the external opening of the follicle. The old hair has, in the mean time, been separated from the papilla and become completely horny, owing to its loss of nourishment, and, being pushed upward by the new-formed hair, falls out when the external surface is reached. In this way the temporary hairs are replaced by the permanent ones, and an entirely similar procedure is furthermore constantly seen repeating itself, even in adults.

General Characteristics.—The hairs, which are modifications of the epidermis, are found in greater or less amount over the entire body, with the exception of the palms of the hands, the soles of the feet, the vermilion border of the lips, the glans penis, the labia minora, and inner surface of the labia majora. Over the majority of the surface they are short, rather colorless, having the character of the embryonic hairs, and hence are termed

the lanugo hairs; but on the head, the eyebrows and the eyelids, in the axillae, on the pubes, and in the male sex on the cheek and upper lip, they attain a much higher grade of development.

The hairs which are present upon the scalp, eyebrows, and eyelids become gradually more marked, thicker, and longer after birth, but at the age of puberty the hairs on the pubes and in the axilla, and the beard in the male, begin to develop and to increase rapidly. Hair also is found around the anus in the male. It is not unusual to see, in certain races, that in women, as they approach and pass the climacteric, a stronger growth of hair appears on the upper lip and face.

The hairs, both the lanugo and the fully developed ones, are for the most part placed obliquely in the skin and are situated in follicles termed the hair follicles. These latter are sometimes short, the papilla lying high up, or, again, of considerable length, and deep down in the subcutaneous connective tissue. The portion of the hair situated in the follicle is the root, that above the level of the skin, the shaft. At the lower extremity of the root there is a whitish, soft, bulbous enlargement, the hair bulb, which has a concave end that fits upon the conical vascular eminence already mentioned as being the hair papilla.

The hair follicle itself may be divided into three parts, according to its form. From its upper extremity, where it opens out upon the surface of the skin, it descends, shaped like a funnel, as far down as the opening of the duct of the sebaceous gland. It then becomes narrowed for a short distance, but broadens again near the papilla to receive the hair bulb.

The hair shaft varies considerably in shape, being in some cases round, in others much flattened, or again angular.

On cross section the hairs are either round, or oval, or triangular, or square, having convex or concave sides.

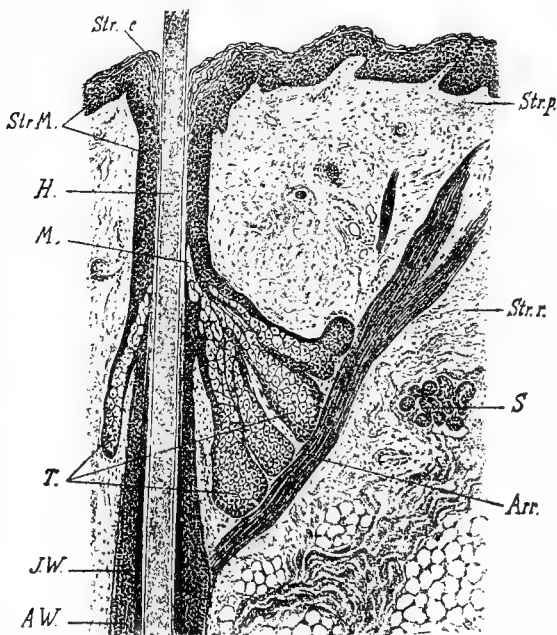


FIG. 5247.—Hair of an Adult at its Point of Emergence from the Scalp. Specimen hardened in Mueller's fluid and stained with hæmatoxylin and eosin. Magnified 50 diameters. (After Rabl.) *H.*, Shaft of hair; *J.W.*, inner sheath of root of hair; *A.W.*, outer sheath of root; *T.*, sebaceous gland; *M.*, outlet of this gland; *Arr.*, arrector pili; *Str.c.*, stratum corneum; *Str.M.*, stratum Malpighii; *Str.p.*, stratum papillare corii; *S.*, sweat gland.

The angular and flattened hairs are found in those localities where the hair is curly, the round ones where it is straight.

At its free external end the hair is pointed when in its natural state, but owing to the fact that it is continually subjected to mechanical influences, such as rubbing, etc., it is usually found to have a more or less rounded extremity.

Histology of the Hair and of its Follicle.—Hair Follicle.—The hair follicle is represented by a sac-shaped cavity composed of connective tissue. At its lower end, which is more or less deeply situated in the cutis, an eminence is seen, analogous to the papillæ in the upper portion of the corium, which is known as the hair papilla. This body, upon which the concave extremity of the hair root is accurately fitted, is oval in shape, and at its base is a distinctly marked constriction—the neck of the papilla. It is composed of connective tissue, similar to that of the cutis, of which it is a part, and contains blood-vessels. (See also Fig. 5233.)

The hair follicle envelops the lower two-thirds of the hair and of its sheaths, but above the openings of the ducts of the sebaceous follicles it is not demonstrable as a separate formation, becoming lost in the tissue composing the papillary body. It consists of three coats. The most external of these is a portion of the cutis proper, and is composed of connective-tissue fibres, which are closely bound together and run longitudinally in the axis of the hair, and is quite rich in connective-tissue cells. In it are distributed the blood-vessels and nerves supplied to the hair. The next innermost coat is composed of elements similar to those which are found in the most external, but they are arranged in a circular manner running around the hair follicle. There are many nuclei found in this coat, the long axes of which are directed parallel with the course of the fibres, and they resemble very strongly the nuclei seen in unstriated muscles; but this resemblance is in all probability due to the tension to which the fibres are subjected.

The innermost of the coats of the hair follicle is a hyaline basement membrane, which has a glassy, transparent appearance. It is in immediate contact with the cylindrical layer of epithelial cells belonging to the external root sheath of the hair. It is not always demonstrable, varying greatly in thickness, and is most clearly marked in the lower third of strongly developed hairs. In the lanugo hairs the connective-tissue envelope of the hair is absent, the root sheaths being derived from the epidermis forming the hair follicle.

The Hair Sheaths.—The root of the hair proper is in the greater portion of its extent covered by an envelope, which consists of several layers of cells very adherent to it. It constitutes the inner root sheath of the hair, and lies in contact with the external root sheath, by which it is separated from the connective-tissue envelope of the hair follicle.

The Hair Proper.—When a fully developed hair is examined under the microscope, it can be seen that it is composed of three tissues, which differ from each other in appearance. These three portions are termed the cuticula, the cortex, and the medulla. Each of these can be easily recognized in the shaft of the hair, but not so readily at the bulb. Still, if the hair is treated with picrorcarmine, the cuticula can be traced here, and it can be seen that it starts from the neck of the hair papilla (Unna). By the same method, it is also found that the cortex develops from the lateral portions of the papilla, and the medulla from the apex.

The Cortex.—The most voluminous portion of the shaft of the hair is constituted by the cortex, a transparent fibrillar mass of varying color. In it are seen dark spots and longitudinal streaks, which are situated between the horny elements of the hair, and are caused by the presence of air. Pigment granules are also present in greater or lesser quantities.

When the hair is treated with sulphuric acid the cortex breaks up into the fibres of which it is composed, and, if the action of the acid has been long continued, it may even separate into long, narrow, spindle-shaped plates. In the centres of these latter an indistinct linear figure is oftentimes traceable. It represents the remains

of the nucleus of the cell from which the plate was derived.

The development of the hair from cells is very distinctly seen at the papilla. The portion of the hair in immediate contact with this body is hollowed out or concave in shape, and it is composed of a row of cylindrical epithelial cells entirely similar to those forming the basic

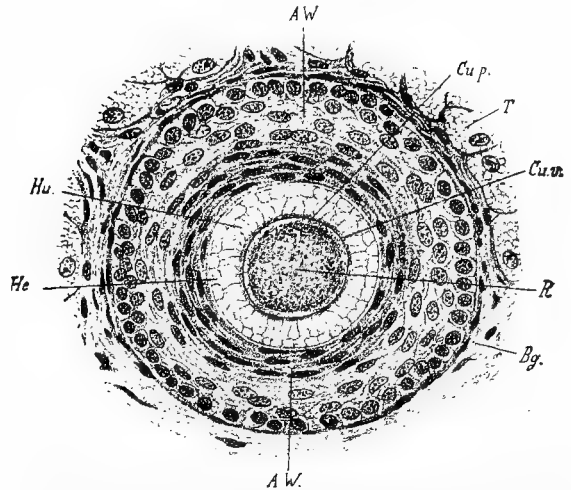


FIG. 5248.—Cross Section of a Hair and its Sheath, from the Scalp. Specimen hardened in Mueller's fluid and stained with hæmatoxylin and eosin. The cut was made at the level of the region in which lie the sebaceous glands. Magnified 250 diameters. (After Rabi.) R, Cortical portion of the hair shaft (the medullary substance is lacking in this specimen); Cu.p., cuticula of the hair; Cu.v., cuticula of the sheath of the root; Hu., Huxley's layer; He., Henle's layer; A.W., outer sheath of the root; Bg., connective tissue; T, sebaceous glands.

layer of the epidermis. This layer of cells is termed the matrix of the hair, and it is upon it that the growth of the hair depends. Starting from this point, it can also be seen how the cells and their nuclei grow longer, become finely fibrillated and granular, and finally, when entirely horny, appear as small plates. These successive changes should be studied on hairs which are little pigmented, for in them they can be seen much more easily than when the opposite is the case. The cells of which the cortex of the hair root is formed have been found by Waldeyer to be composed of small fibres. Each cell is united to the contiguous ones by short spines, in a manner analogous to the cells composing the epidermis.

The pigment which gives the hair its various shades of color is an important constituent of the cortex. It varies greatly in quantity, and in proportion to its abundance or comparative absence the hair is dark or light in color. It occurs both in a diffuse form and also in granules. The elements of the cortex are diffusely pigmented by the former, but the pigment granules are distributed here and there, and are situated in and between the cells composing the cortex (Waldeyer). This deposition of the pigment granules in the cells is most clearly seen in the root of the hair. The source of the pigment is not yet fully established, though Riehl and others more lately have thrown some light on the subject. In the tissue of the papilla of the hair irregular-shaped nucleated cells, the protoplasm of which contains a considerable amount of pigment, have been found. They were present as far up as the matrix of the hair, between the cells of which they sent long prolongations, and they could also be traced higher up as fine intercellular pigment deposits. Riehl also observed that the cells of this portion of the hair root, which were not yet horny, contained granules of pigment around their nuclei, and also that the cells of the matrix were quite closely connected with the prolongations of the wandering pigment cells of the hair papilla, from which their protoplasm took up pigment granules. In regard to the source of these

granules. Riehl argued that, inasmuch as wandering pigment cells were regularly met with in the papilla of the hair and following the course of the blood-vessels, the blood must be the source of the pigment, and this latter must be carried by the cells to the hair.

The Medulla.—The medulla is situated in the axis of the hair throughout almost its entire length, but it narrows and terminates at some distance from the free end. It is marked in the stronger hairs, but is usually absent in the lanugo hairs, and often also in those of the scalp. The presence of the medulla is shown by a more or less broad, longitudinal band of a dark color, which is due to the air situated between its composing elements. These latter are cells which are shrunken into irregular shapes, possess no nuclei, and are furnished with spines and prongs (Waldeyer).

At the bulb of the hair, the medulla differs very slightly from the cortex. Over the apex of the papilla and above the cylindrical cells situated there, which represent the matrix of the medulla, large nucleated cells are seen, and in their protoplasm are large drops of keratohyalin. In proportion as the shaft is ascended, these cells become shrunken, harder, lose their nuclei, and the keratohyalin disappears. They are bound together by means of the spines and prongs on their surface, between which are left spaces—intercellular spaces. Below the external surface these spaces serve as channels through which nourishment is furnished to the young cells of the medulla, but where the hair is exposed to the external atmosphere this fluid evaporates, and the spaces become filled with air.

The Cuticula.—The hair is also furnished with a cuticula, which surrounds the greater part of that portion of the hair which lies in the follicle. It is formed by a layer of horny plates, arranged like tiles on a roof, and they are closely bound together. The cuticula originates from the neck of the papilla of the hair, between the matrix of the cortex and that of the inner root sheath. At this point it consists of several rows of cylindrical nucleated cells, which divide soon after leaving the matrix into two layers. One of these goes to form the cuticula of the hair, the other the cuticula of the inner root sheath. The cells of the former are at the middle of the hair papilla, directed perpendicularly to the circumference of the hair, but gradually become more and more inclined toward it. At the upper portion of the hair follicle the cuticula is no longer distinguishable and becomes a constituent portion of the cortex. At the matrix the cells are epithelial in character, but they become transformed into solid transparent horn plates without nuclei.

The Root Sheaths.—The hair root is further enveloped by two coats—the root sheaths—which are closely adherent to it. They are known individually as the inner and the outer root sheath. The former is immediately around and in contact with the hair, and ends within the hair follicle; the latter, more external, passes up to the orifice of the follicle, where it becomes continuous with the spiny layer of the epidermis.

The Inner Root Sheath.—The inner root sheath is composed of three layers—the cuticula, the one nearest the hair, Henle's layer, the most external, and between these two Huxley's layer.

The cuticula of the inner root sheath arises from the same matrix at the neck of the hair papilla as the cuticula of the hair. The cells composing it are so arranged that their long axes are parallel to the circumference of the hair, that is, in an opposite direction to the cells forming the cuticula of the cortex. They undergo transformation in a manner entirely analogous to the one which has been already described for the cuticula of the cortex. The cuticula of the inner root sheath is lost sight of within the follicle, becoming a part of the sheath.

The Layers of Huxley and of Henle.—The portion of the inner root sheath which is situated between the cuticula just described and the external root sheath is composed of the two layers known as those of Huxley and of Henle. They also take their origin from the neck of the papilla, and at that point appear as a layer of three or

more cylindrical epithelial cells. Drops of keratohyalin, however, appear very soon in these cells, and this substance increases rapidly in quantity. The change in their appearance due to the presence of the keratohyalin is very marked on a level with the apex of the papilla, and the cells are seen here to have attained a much larger size. The cells forming the layer of Henle—the most external—contain, however, a greater amount of keratohyalin, and undergo hornification much more rapidly than they do in the layer of Huxley. Consequently, Henle's layer is found represented by horny, polygonal, non-nucleated elements at a much lower level than Huxley's layer. This latter, the inner portion of the inner root sheath of the hair, is composed of the papilla of cells which contain a smaller amount of keratohyalin. Keratification in them is not so rapid as in the cells of Henle's layer, the nuclei do not disappear so early, and the complete transformation of the elements of Huxley's layer into horny masses occurs at a higher level than is seen in the former one. The inner root sheath ends in the hair follicle.

The External Root Sheath.—In describing the embryology of the hair, it was stated that the first changes observed consisted in a proliferation and prolongation downward into the cutis of a portion of the cells forming the stratum spinosum of the epidermis. The further steps which occurred in the evolution of the hair, and which took place in the central portion alone of this prolongation, it has also been seen, resulted in the formation of the shaft of the hair, but the remaining portion also serves an important purpose. It represents the external root sheath, or envelope, of the hair, and is separated by it from the connective tissue composing the follicle.

The outer root sheath is not uniform throughout its entire extent, but is lined on the surface next to the hair shaft, and as far down as the opening of the duct of the sebaceous gland, by the stratum corneum and stratum granulosum. From here to the level of the hair papilla the stratum spinosum descends in its entirety, but then narrows, and at the neck of the papilla is reduced to a layer of two or three cylindrical cells. It lies at this point in close contact with the cells from which the inner root sheath is formed.

The appendages of the hairs are the sebaceous glands, and bundles of unstriped muscular fibres are also attached to them. They have been, however, already described.

George T. Elliot.

SLEEPING-SICKNESS.—**ETIOLOGY.**—Manson's former theory of sleeping-sickness being caused by the *Philaria perstans* (see Vol. VII., p. 242) is now regarded as untenable, as there are regions in which the filaria abounds and sleeping-sickness is unknown, and likewise places given over to sleeping-sickness in which the filaria has not been found.

Castellani found trypanosomes in the cerebrospinal fluid in cases of sleeping-sickness; and this has been subsequently verified by numerous other observers. It is now recognized that this trypanosome—*Trypanosoma gambiense*—is the cause of the disease, and that it gains entrance to the body through the bite of the *Glossina palpalis*, one of the species of the tsetse fly. Besides being found in the cerebrospinal fluid, it is also found sometimes in the blood. It is not yet settled whether the *Glossina palpalis* is a true intermediate host or simply a carrier of the trypanosome. Just how the trypanosome produces the pathological changes observed in this disease, is also at present unknown; but Mott (Report of the Sleeping Sickness Commission, No. VII.), after an extensive study of the pathology of sleeping-sickness, comes to the following conclusion: "All cases of sleeping-sickness have trypanosomes in the cerebrospinal fluid at some time or other, and it is probable that the entrance of the trypanosomes into this fluid marks the onset of, and slowly causes, the chronic inflammatory change in the lymphatic system of the central nervous system. The alternative hypothesis is that the trypanosomes, by multiplying in the lym-

phatic glands, produce a toxin which is absorbed by the lymphatics, and this toxin proceeds along the vessels and nerves to the lymphatics of the cerebrospinal axis, the route being especially from the cervical glands by the lymphatics of the large vessels and nerves entering the base of the skull."

Koch has recently claimed that the crocodile is an important factor in the spread of sleeping-sickness, in that the *Glossina palpalis* lives chiefly on the blood of these animals. This claim, while interesting, is not proven; and it has been pointed out that whereas crocodiles are common all along the banks of the Nile, sleeping-sickness is found only in the upper reaches; crocodiles are also plentiful in other districts which are free from sleeping-sickness.

DIAGNOSIS.—This can now be accomplished with certainty by examining the cerebrospinal fluid and the blood, in one or both of which fluids the trypanosome will be found. About 10 c.c. of the cerebrospinal fluid should be withdrawn by lumbar puncture, then centrifuged for ten or fifteen minutes, and the sediment examined with a one-sixth or one-eighth objective. The blood can be examined directly; if this should prove negative, it ought to be supplemented by a further examination as follows: withdraw 10 c.c. from a vein, add one c.c. of sodium citrate, then centrifuge for ten or fifteen minutes, and examine the sediment in a hanging drop or in a smear. A. R. Cook recommends Greig's method of diagnosis. This consists in puncturing the swollen cervical glands; in the fluid contained therein the trypanosome can generally be found, with a one-eighth objective.

PROPHYLAXIS.—At present much more investigation is necessary, and many problems have to be solved before any certain prophylaxis can be promised. It is, however, safe to say that (1) the tsetse fly must be either destroyed or prevented from reaching the inhabitants; (2) those who are infected must be strictly isolated so that the trypanosome cannot be carried to others; (3) the healthy or non-infected must be protected both day and night from attacks of the *Glossina palpalis*, and all tsetse flies must be always regarded as dangerous and undesirable; (4) the districts in which the *Glossina palpalis* breeds should, as far as possible, be cleared of all bushes, undergrowth, weeds, etc.; this can be accomplished either by cutting down or by burning. The details of prophylaxis and quarantine for each locality can be set forth best (if not only) by the authorities who have the power to enforce such regulations as may be considered necessary.

TREATMENT.—Atoxyl (as first pointed out by Thomas, of Liverpool) gives by far the best promise of success in the treatment of sleeping-sickness. It is not claimed that this agent is absolutely curative, much less that it is a specific; but it gives considerable relief to the patient and decidedly ameliorates the symptoms, even to causing the disappearance of the trypanosomes from the cervical glands. Atoxyl is best administered by hypodermic injection in doses of 2 c.c. of a saturated solution (about twenty per cent.) of atoxyl in distilled water; this dose is given every other day for a fortnight. Or half-drachm doses of the solution may be given *per os* for two successive days, this dose to be repeated at intervals of ten days and continued in this way for several months. The details of the results obtained with this preparation vary considerably in the reports from the different observers, the most optimistic being that of Koch, who claims to have reduced the death-rate to eight per cent.—a truly remarkable record in a disease generally regarded as almost invariably fatal.

Serum treatment and a synthetic product "trypan-roth" have also been recommended, or at least suggested; but up to the present atoxyl seems to be the recognized remedial agent.

R. J. E. Scott.

SNAILS.—A popular term applied to those forms of the gasteropod mollusks, belonging chiefly to the order *Pulmonata*, which are provided with a shell. They are

divided into the land, fresh-water, and marine species, belonging respectively to the suborders *Geophila*, *Limnophila*, and *Thalassophila*. There are some few terrestrial species and a large number of fresh-water and marine forms, belonging to the order *Azygobranchia*, to which the term snail is also sometimes applied. The fresh-water and marine forms are perhaps more commonly known as periwinkles and whelks, while allied genera not provided with a shell are ordinarily spoken of as slugs.

The order *Pulmonata* is characterized by a lingual membrane provided with numerous teeth arranged in many uniform transverse rows; mouth usually supplied with one or more horny jaws, a respiratory organ in the form of a closed chamber lined with pulmonic vessels on the back of the animal and covered by the shell when present; the edge of the mantle being attached, and the entrance to the air chamber being through an opening in the side closed by a valve. The operculum is almost universally absent. The tentacles and eye peduncles are retractile or contractile. The shell varies in form, and is sometimes rudimentary or wanting. They are hermaphrodites, with reciprocal impregnation, generally oviparous, and all forms, whether terrestrial, fluviatile, or marine, respire free air.

The American species of terrestrial snails live mostly in the forest sheltered under the trunks of fallen trees, layers of decayed leaves, stones, or in the soil itself. They are, as a rule, solitary in their habits; only exceptionally, as sometimes in the early days of spring, do they congregate in considerable numbers in warm and

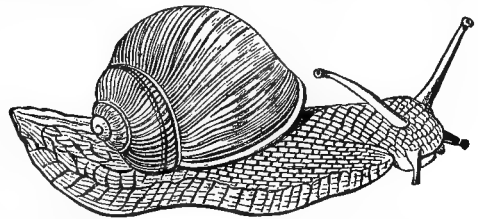


FIG. 5249.—*Helix Pomatia* Linn.; the European Vineyard Snail, the one most extensively eaten. (From Kieferstein.)

sunny situations, but these assemblies do not last more than a few days; they then scatter and again resume for the rest of the year their solitary mode of living. They are rarely seen abroad except on damp dark days or at twilight, and, indeed, they almost disappear as the forests are cut down, and seem to flee the approach of man. The European species, on the other hand, follow in the track of cultivation and are common in gardens and fields, on walls and hedges, and other places exposed to the action of light. It is probably owing to this radical difference in their habits of life that the large majority of our species are so plain and uniformly dull-colored, while the European species are brightly colored. In size the snails vary from those minute species a quarter of an inch or less in length to the gigantic African species belonging to the genera *Achatina* and *Balimus*, which sometimes attain the length of eight inches.

The eggs are laid in the early spring. Some few forms are viviparous. As soon as hatched, which takes place in from twenty to thirty days, the young snail devotes himself strictly to the business of eating. He first devours his own shell, and then, according as his instinct leads him, begins on either vegetable or animal food. The majority of them prefer vegetable food, though it is certain that

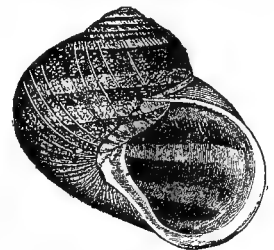


FIG. 5250.—*Pomatia Aspersa*. (From Binney.)

some forms are also fond of animal food, and sometimes prey upon earthworms, their own eggs, or even upon each other. The amount they can eat is enormous, as can well be testified to by the gardener, who often finds a whole field of vegetables almost destroyed in a single night. As might be expected from this, their rate of growth is very rapid, and they frequently double in size within a week. At the first approach of frost they retire into secluded and sheltered spots under logs or stones, or partially burrow into the soil, withdraw into their shells, and dispose themselves for their annual sleep or hibernation, only to be awakened again in from four to six months by the warmth of spring.

They possess the power of secreting a mucus-like material from the general surface of the body at will. The slugs have this function developed to a much greater degree, and it is used by them as a means of defence. Whenever a foreign substance touches them they secrete a quantity of the mucus, which forms a kind of membrane interposed between themselves and the irritating substance. This mucoid material is a non-conductor of heat and impervious for a time to liquids, so that by its means they are enabled for a considerable time to withstand the action of corrosive gases, alcohol, and even boiling water. The fresh-water and marine forms live on the rocks and aquatic plants at the bottoms of ponds and rivers, and along the seashore, where they may be seen in immense numbers when at any time, as at ebb-tide, the rocks are exposed.

There are a large number of species of snails which have been used as food. Most of these belong to the genus *Helix*, of which more than twelve hundred species have been described. Few of the American forms have been so used, partly for the reason that it has never become the custom here, and partly, probably, from the curious fact, already mentioned, that the forms indigenous to this country are mostly solitary and do not collect in herds or communities. Many of the European species, on the contrary, herd together in immense numbers and so are very easy to collect and peculiarly adapted to colonization. The "edible snail," *Helix pomatia*, is the one most commonly eaten in Europe, but *H. aspersa* and *H. hortensis* are also very generally used. The first of these has, I believe, never been introduced into this country, but *aspersa* and *hortensis* both have been, and are now found in considerable numbers in certain localities. They retain their habits of congregation, and will no doubt in time be much more generally used as an article of diet than they are at present.

The ancient Greeks and Romans regarded snails as one of their greatest delicacies, and imported them from all parts of the then known world to be reared and fattened in their extensive snail ponds. In many parts of Africa the large species which are indigenous there are used as a daily food all the year round. At the present time in Austria, France, Switzerland, Spain, and Italy, the collection, rearing, and preparing them for market afford occupation to a large number of people. An idea of the extent of the industry may be gained from the fact that from Ulm alone some four million are annually exported, and about ninety thousand pounds are sold in the Paris markets every year.

The wild snails are collected and placed in small plots of land cleared of trees and covered with heaps of moss and pine-twigs, and separated from each other by moats, or trails of sawdust, for which snails have a natural antipathy. They are kept here and fed on fresh grass, cabbage leaves, mint, and other aromatic herbs. In the course of a week or ten days they have become quite obese and, besides, have attained a very delicate flavor; they are then starved for a few days to allow them to get rid of excrementitious matter, when they are ready for the market. To prepare them for the table they are well washed, then broiled, baked, or boiled, shell and all, when they are either extracted and served with various suitable sauces, or are placed on the table entire, to be removed at the time of eating by placing the shell to the mouth and drawing out the animal by sucking it.

The sea snails are not so extensively used as food, though in England the common periwinkle (*Littorina littorea*) is consumed in immense quantities by the poorer classes on the coasts as well as in London. About three thousand tons of them, valued at £15,000, are annually shipped to London alone.

There has been a number of cases of poisoning from eating snails which have been allowed to feed on hemlock and belladonna, so that now there has been an inspector appointed in Paris whose business it is to see that they are in fit condition for consumption.

In some persons the ingestion of snails brings on marked attacks of urticaria—the same as is seen in certain cases after eating clams, oysters, and other shell fish. In these cases it will be understood that there is a more or less marked idiosyncrasy in the person.

An idea of the nutritive value of these mollusks may be gained from the following analysis of the "edible snail," made by Mr. Charles Mene:

Water.....	72.747
Nitrogenous matter.....	17.652
Fatty substances.....	1.125
Non-nitrogenous matter.....	6.300
Salts.....	2.176
Nitrogen.....	2.823

In some parts of the world the snail has more or less of a reputation as a "cure" for consumption, concerning which it is only necessary to say that it may be considered a food of some value as affording a change of diet.

William Barnes.



Fig. 5251.—*Tachea hortensis*. (From Binney.)

STOVAIN is benzoyl-ethyl-dimethylaminopropanol hydrochloride with the structural formula $C_{14}H_{22}O_2HCl$. It is a hydrochloride of amylene, a derivative of amino-alcohol. It crystallizes in small scales which melt at 175° C.; is freely soluble in water, dilute alcohol, and acetic ether; only slightly soluble in absolute alcohol. Aqueous solutions are slightly acid in reaction to litmus, are precipitated by all alkaloidal reagents, and decompose when boiled at 120° C.

Stovain is a local anæsthetic, a substitute for cocaine, which it resembles in its physiological action. It is claimed that the anæsthetic power of stovain is equal to that of cocaine; that it is, like cocaine, a vaso-dilator rather than a vaso-constrictor, and that it is from one-half to one-third as toxic as cocaine, slightly antiseptic, and germicidal. It is not an anodyne when administered subcutaneously, but produces analgesia when used in epidural or epidermal injections, especially so in the neuralgias, including sciatica. Concentrated solutions sometimes cause tissue injuries, and this may be followed by gangrene. In ocular surgery when it is used in sub-conjunctival injections, anæsthesia is said to be complete in one minute or even in some instances less than a minute. When used by instillation it causes epithelial desquamation to some extent, as does cocaine. When applied in powder form to the eyes of rabbits it has produced leucoma.

Stovain has been used in dentistry preceding extractions, but instances have been reported in which its use was followed by distressing symptoms, even syncope. Stovain has been extensively used abroad in lumbar anæsthesia. In some instances its use has been accompanied or followed by malaise, nausea, vomiting, persistent headache, and even collapse, although such effects when they do follow rarely become dangerous.

The dose of stovain is uniform with that of cocaine. Solutions should be sterilized by heating to 105° or at most 110° C., and should be injected under or into the derma. When borated water is used to sterilize the syringe preceding injections, the syringe should be thoroughly rinsed in distilled water before drawing in the stovain solution.

John W. Wainwright.

STYPTOL (cotarnine phthalate) is represented by the formula, $C_6H_4(CO_2H)_2 \cdot (C_{12}H_{11}NO_2)_2$. It is a

yellow crystalline powder, readily soluble in water, comprised of about 75 per cent. of cotarnine and 25 per cent. of phthalic acid. It is recommended principally as a styptic, although sedative properties due to the cotarnine content are claimed. It is used locally in bladder and uterine hemorrhages; does not produce contraction of the uterine muscles; produces a slight drowsiness. Styptol can be used instead of ergot or ergotin as a hæmostatic. It is used also preceding menstruation in menorrhagia, metrorrhagia, and dysmenorrhœa, and in hemorrhage during the menopause, pregnancy, or from fibroma and myoma of the uterus. Dose, 0.05 grm. ($\frac{1}{4}$ grain) three times a day.

John W. Wainwright.

SURGICAL OPERATIONS, COMPLICATIONS AND ACCIDENTS FOLLOWING.

—But little literature of a concise nature has as yet appeared upon this important and neglected subject. One reason for this undoubtedly has been that the complications of postoperative work have been steadily growing less in frequency and in severity, owing to the introduction of asepsis and improved technique. Nevertheless the very popularizing, if it may be so called, of intricate and difficult surgical work by the flood of modern surgical literature, as well as by the teachings of the masters, is in itself sufficient ground for the presentation in equally assimilable form of the dangers, both local and general, which every patient operated upon is subjected to, and which dangers form an index of the responsibility of the men who operate.

SHOCK.—Perhaps the most general complication following operation is shock. It may be described as a vasomotor disturbance which manifests itself clinically by a dilatation of the abdominal veins. Many therapeutic measures have been invoked to protect the patient from this condition. Prominent among these may be mentioned the cording of the extremities, Crile's pneumatic operating suit, and, most recent of all, the transfusion of blood, which has been made possible by the advanced surgical work upon the vessels. These mechanical aids to the recovery of the vasomotor balance should be seconded by an intelligent use of certain drugs. In addition to the usual cardiac stimulants, adrenalin chloride has been found in certain cases to have a selective and favorable action. It is not to be doubted that the patient's mental condition is an important factor that should be taken into account when estimating the probable degree of shock from certain operative procedures. This was strongly believed in by Fowler, and Estes considers the individual equation of the patient to be a most important and hitherto neglected subject. One of the most valuable contributions to the prevention of shock has been made by Crile, who has proved that preoperative cocaine injections into the nerve trunks of the seat of operation tend to lessen operative shock.

Shock once established is to be treated by posture, by artificial heat, by intravenous infusion, by hypodermoclysis, and high enemas given at 120° F. and containing whiskey and coffee.

SECONDARY HEMORRHAGE.—Widely removed from shock, yet resembling it, often with a closeness which is fatal to the patient, is this somewhat uncommon, but by no means unknown, complication. Much has been written on the differential diagnosis of the two conditions, but the cardinal point of difference between the two, which shall hold true in every case, has yet to be determined. Obviously the treatment of hemorrhage consists in a reapplication of the slipped ligature. Fortunately this complication is rarely met with outside of the abdominal cavity.

ANURIA.—The etiology of postoperative anuria is not in all cases thoroughly understood. It is usually ascribed to the awakening of a dormant nephritis owing to the irritation of the anæsthetic. It is probable, however, that the elimination through the kidneys of certain metabolic products which have failed to complete the usual and physiological metamorphic changes

is a factor in the production of anuria in at least a number of cases. That certain of these bodies which are toxic to the kidneys and inhibitory to their action are present in the normal body fluids—bile, for example—is highly probable.

Our lack of knowledge of the precise etiology of postoperative anuria renders the treatment necessarily empirical. The indication, however, is clear. The kidneys should be flushed with water as rapidly as possible, and every other avenue of excretion should be cleared for action. Thompson and Kemp have obtained remarkable results by the introduction through hypodermoclysis of saline solution directly over the region of the kidneys. Continuous rectal irrigation, however, of salt solution at 120° F. is probably productive of the most good. Dry cups are often applied over the renal region. In chosen cases surgical intervention is clearly indicated, for a return of function often follows decapsulation or nephrotomy.

PNEUMONIA.—This complication is not infrequent. It may be caused by exposing the patient to cold either upon the surface of the body or internally from the inhalation of chilled anæsthesia vapor. It is not so frequently of the type commonly designated lobar pneumonia, and due to the pulmonary invasion of the *Micrococcus lanceolatus*, as that usually described as hypostatic or septic. The hypostatic is a mechanical affair traceable to one of two conditions, viz., (1) keeping feeble patients too constantly in a recumbent position, and (2) a failing heart. Septic or deglutition or inhalation pneumonia is caused by the inspiration of vomited food particles or septic agents during anæsthetization or after operations about the mouth and throat. It may result in gangrene of the lungs.

The treatment depends upon the type of pneumonia present. It embraces the well-known methods prescribed for that disease.

VOMITING.—Vomiting which persists after twenty-four hours, particularly if the anæsthetic has been given according to modern methods, is apt to prove a serious postoperative complication. This not infrequently may be of hysterical origin, and is to be treated as such unless some definite physical cause for it can be discovered. Aside from the vomiting which may follow certain intracranial operations, and which may be ascribed to intracranial pressure, probably the most potent cause of persistent postoperative vomiting lies in acute dilatation of the stomach. The etiology of this is explained by the slipping of the small intestine down into the pelvis owing to relaxation of the tissues brought about by prolonged anæsthesia and excessive preoperative purgation. The superior mesenteric artery and the mesentery, if the patient be left continuously in the dorsal position, both drag tightly across the duodenum, thus blocking the exit of the stomach. This organ, affected by the same relaxing causes already referred to, loses its tone and dilates. The treatment for this condition consists in turning the patient upon the abdomen in order to relieve the tension and provide an exit for the contents of the stomach; in hot and copious irrigations of the organ by lavage; sometimes in the introduction of selective drugs such as cocaine or carbon dioxide gas which act as soporifics locally, or cerium oxalate, the action of which is unknown, but sometimes specific.

THROMBOSIS.—As a postoperative complication after laparotomy this is reasonably common. In 3,334 cases of appendicitis thrombosis occurred in 29 (Groves); in 7,130 it occurred in 48 (Schenck). It is well known that the left lower extremity is the most frequent seat of peripheral thrombosis, and it has been suggested that this is due to the fact that the left common iliac vein is crossed almost at right angles by the left internal iliac artery. The right common iliac artery also touches it. In the case of the right vein no such source of pressure can be found. A further source of pressure on the left side may have its origin in the loaded sigmoid. Regarding the etiology of thrombosis the reader is referred to an article on "The Surgery of the Blood-Vessels" in

the present volume. Suffice to say here that, clinically, post-operative thrombosis does not appear as a rule to be associated with infection. Anæmia predisposes to it by increasing the carbon dioxide in the blood.

The treatment of postoperative thrombosis, if carried out according to most recent technique, resolves itself into a localization of the thrombus, an opening of the vessel, a removal of the clot, and the subsequent re-suturing of the organ. This method will have more brilliant possibilities when we have a better knowledge of the cause of thrombosis, and more accurate means of locating the lesion. The accepted method of treatment consists in six weeks' rest in bed and in giving a diet which shall diminish the coagulability of the blood. Some of the materials which affect this are: oxygen, alcohol, abundant quantities of fluid, citric acid, limited solid food, tobacco smoking, fruits, and wine. A bandage should be kept on the extremity for at least six months, and massage and other exercises should be employed to dilate the unobstructed deep veins.

ACUTE CARDIAC DILATATION.—In most of the cases reported of sudden death following operation and which were ascribed to acute dilatation, no cardiac lesion prior to operation was made out. This coupled to the fact that at autopsy no lesion of whatsoever nature could be found, either in the heart or elsewhere, and further to the fact that death in these little-understood cases has occurred toward the end of a seemingly uneventful convalescence,—all this has led to very grave doubt as to the relationship between death and the moderate degree of cardiac dilatation found at autopsy. Operators of such wide experience as Richardson and Fowler state that in their opinion the cause of these sudden deaths is unexplainable. There can be therefore no prophylactic treatment suggested.

SEPSIS.—This is a general systemic disturbance resulting from the introduction of pyogenic organisms into the body either through defective technique from the outside, or by the liberation of such organisms from localized foci within the patient at the site of operation. The general conditions resulting from such an invasion are well known. The first indication for treatment is the removal of the cause. The use of special vaccines may or may not be indicated.

ACIDOSIS OR ACETONÆMIA.—This condition is exceedingly rare in non-diabetics as a postoperative complication. Brewer reports in the *Annals of Surgery*, xxxvi., p. 481, one case which terminated fatally. He says, "Of the autointoxications, three varieties must be considered,—ptomaine poisoning, uræmia, and acetonæmia. Neither the acetone nor the diacetic and β -oxybutyric acids are responsible for the symptoms of delirium and coma, for animal experimentation has shown them to be harmless. The actual cause of the symptoms probably depends upon the fact that the presence of these three bodies reduces the normal alkalinity of the blood, diminishes its carbon dioxide carrying power, and thus overcomes the individual by rapid carbon dioxide poisoning."

The symptoms are sweet ethereal odor of the breath, delirium, and rapidly fatal coma.

While acidosis is recognized as a frequent complication of diabetes, it has recently been shown to occur particularly in children in the course of sepsis; of sapræmia; of brain and spinal lesions; of starvation, particularly deprivation of carbohydrates; and as a result of general anæsthesia both from chloroform and ether.

LOCAL COMPLICATIONS.—Under modern aseptic conditions and after the employment of proper technique, which signifies a minimum injury to the tissues, it is conservative to say that local infection occurs in less than one per cent. of all clean cases. Such infection implies a healing by second intention. Infection, however, is not the only cause for the failure of primary healing; faulty technique, causing areas of ischæmia, as well as a debilitated condition of the tissues being among the prominent predisposing factors.

AIR AND FAT EMBOLISM.—The entrance of air into

the circulation is occasionally caused by the accidental puncture of one of the large veins. It can be controlled immediately by the filling of the wound space with sterile salt solution which takes the place of the air until the wound can be closed.

Owing to the frequent use of paraffin injections for the relief of certain deformities, it should be noted that fat emboli have at the time of operation found their way into the circulation and have lodged in the neighboring artery. The prophylaxis of this alarming condition is to use a paraffin of high melting-point.

POSTOPERATIVE RASHES.—These are usually the result of wound infection, although this does not always hold. Mummery gives the following points to aid in distinguishing a septic from a scarlet-fever rash: (1) The premonitory febrile symptoms are usually absent, the rash being the first thing noticed in most cases. (2) The distribution of the rash is irregular; it appears, often simultaneously, all over the body, and not, as in scarlet fever, on the neck and face first. (3) There are no throat symptoms except in those cases where the wound is in the throat. (4) The pyrexia is high and of the septic type, often with marked intermission.

POSTOPERATIVE INTESTINAL PARESIS.—It is often difficult to differentiate this condition from peritonitis. It may be of the so-called dynamic type or of the paralytic type. Obviously the two conditions should be given very different forms of treatment.

J. W. Draper Maury.

TEPLITZ.—Teplitz, or Teplitz-Schonau, is the oldest spa in Bohemia, and lies south of Dresden at a distance of about four hours and a quarter by rail. It is situated in a valley at an elevation of 700 feet, and is surrounded by attractive scenery, affording many pleasant excursions. Not far away is the well-known "Saxon-Switzerland," and near by also is Eichwald, a resort for consumptives, who go for the milk and air treatment. The climate is somewhat variable, still pleasant in summer, but cold late and early in the season.

The waters are of the indifferent thermal type, of a temperature of from 75° to 120° F., similar to those of Plombières, Bath, Buxton, Leukerbad, and many others. The waters contain small quantities of alkalies, the carbonate, sulphate, and chloride of sodium, carbonate of calcium, and a very little lithium and strontium carbonates. So they may be also classed as weak alkaline waters.

The principal method of using these waters is by bathing, and they are applicable to the class of cases which are benefited by the skilful application of warm water accompanied by the careful regulation of one's mode of life.

The diseases treated at Teplitz are chronic gout and rheumatism and allied affections, such as sciatica, lumbago, myalgia, etc.; functional nervous affections; some chronic skin diseases, as eczema, psoriasis, prurigo, pruritus; some forms of secondary syphilis; and slow-healing wounds and ulcers.

The baths are given hot and tepid; the latter are said to be better suited for nervous affections in delicate persons. The hot baths are employed in cases of chronic gout and rheumatism, and the object in view is to promote the absorption of exudates.

There are nine large bath establishments with the usual equipment for applying the waters in various ways. There are also mud or peat baths given at a temperature of about 100° F., which are said to have a very soothing influence. There are free public baths for the poor, and military hospitals for invalid soldiers.

The water is used internally in certain cases, and in the Kurgarten mineral water from other Continental spas is supplied.

The physiological effect of the baths is stimulating when applied hot, and soothing when tepid.

An "after-cure" in the mountains or at the seaside is advised after these baths.

The accommodations are very good, and in nearly all

the bath-houses apartments can be obtained. It is said to be a less expensive place than Carlsbad. The parks and gardens are very attractive, particularly the *Kurgarten* and the *Schloss-Garten*. There are also the usual concerts, music, etc.

Edward O. Otis.

THYMUS GLAND, DEVELOPMENT OF.—The first statements regarding the development of the thymus gland contradicted each other completely. Arnold¹ asserted that it arose in common with the thyroid from

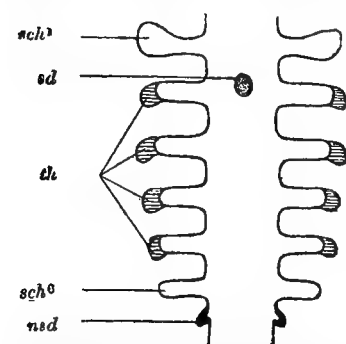


FIG. 5252.—Diagram showing the Branchial Clefts and the Glands arising from them in the Shark. (From Hertwig, after de Meuron.) *sch¹*, *sch⁶*, First and sixth branchial pockets; *sd*, thyroid; *th*, thymus; *nsd*, lateral thyroid.

be entertained when we consider that, for studies of this sort, the methods at that time were very crude; but in spite of all this we are under obligations to Remak for so much light regarding many problems in embryology, and it really seems a pity that his own view, which later on proved to be correct, should have been abandoned on account of his over-caution. By the more improved methods, both Kölliker⁴ and His⁵ observed that the thymus must be of epithelial origin, and therefore accepted the old view of Remak. It may be added that at this very same time two elaborate papers were published by Afanassiew⁶ and Watney,⁷ in which they attempted to demonstrate that the gland arises from the mesoderm. More accurate methods were now introduced, and it soon was demonstrated by Stieda⁸ that in many animals the thymus arises from the third branchial pocket. This was also confirmed by Born⁹ (and many others,^{10, 19}), who in this study introduced his well-known method of reconstruction.

In the third part of his "Anatomie menschl. Embryonen," His⁶ brought forth the view that the thymus

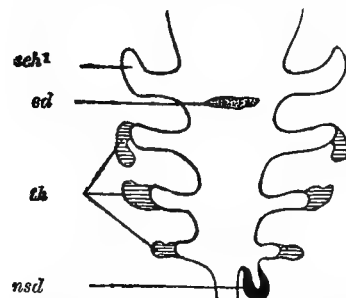


FIG. 5253.—Diagram showing the Branchial Clefts and the Glands arising from them in the Reptiles. (From Hertwig, after de Meuron.) *sch¹*, First branchial pocket; *sd*, thyroid; *th*, thymus; *nsd*, lateral thyroid.

fore considers the origin of the thymus still an open question, and until more careful researches are made, accepts the view of Fischelis²² and of Kastschenko,^{23, 24}

that is, that it arises from both ectoderm and endoderm.

Shortly after the branchial arches are formed there appears at the dorsal side of each cleft a thickening of the ectodermal cells, which soon separate from the endoderm to form distinct groups of glands. This is the condition of things in low vertebrates, and as the scale is ascended certain groups become more and more prominent, until man is reached, when only the two groups from the third branchial pocket remain to form the thymus.

In the fishes the general relation of these glands to the branchial clefts is shown in Fig. 5252.

These individual glands are soon united into one large gland on either side of the pharynx; in the bony fishes these groups unite into one gland before they have separated from the pharynx. In the reptiles the number of glands are reduced (Fig. 5253) to correspond with this number of branchial clefts. Van Bemmelen discovered in the elasmobranchs that the posterior cleft, or rudimentary cleft, produced a distinct body which did not unite with the thymus. This he has termed the suprapericardial body, and later its homology was found in many classes of vertebrates. In many reptiles it is unilateral, as shown in the figure. Considering their origin, they seem to be intimately related with the thymus, but in mammals it is probable that they are added to the thyroid, and will be discussed under that heading.

In birds the third branchial pocket gives the main origin of the thymus, as shown in Fig. 5254. Here we have a sharper line of demarcation between ectoderm and endoderm, as the branchial clefts do not break through as in fishes. We can now state with great certainty from what embryonic layer this gland arises, provided we have good serial sections to study. Very recently Kastschenko discovered a small gland in connection with the second branchial pocket, but as yet its fate has not been determined. It is no doubt a remnant of the portion of the thymus which arises from the same place in lower vertebrates. The third branchial pocket, however, becomes very prominent, grows toward the head, and is at no time blended with the ectoderm (Fig. 5255). To be sure, it comes in apposition with the ectodermal invaginations of the clefts, but recent

work has shown that these have to do with the ganglia of the cranial nerves, and do not unite with the thymus as thought by His and others. Moreover, it is by no means probable that these sense organs of Froriep and Beard should suddenly leave the nerve ganglia in certain regions and unite with glands. Both observations and principles of development contradict this. The fourth branchial pocket, as well as a rudimentary fifth (fossa subbranchialis), gives rise to a few small bodies, the nature of which is not as yet truly known. That from the rudimentary fifth, no doubt, gives the gland which is homologous with Van Bemmelen's suprapericardial body.

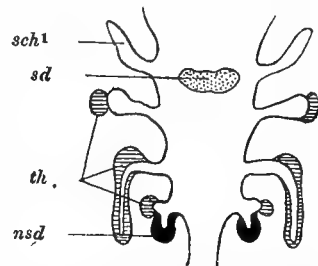


FIG. 5251.—Diagram showing the Branchial Pockets and the Glands arising from them in the Chick. (Modified from de Meuron.) *sd*, Thyroid; *sch¹*, first branchial pocket; *th*, thymus; *nsd*, lateral thyroid.

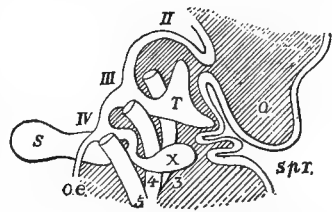


FIG. 5255.—Dorsal View of a Reconstruction of a Chick 110 hours old. $\times 35$. II, III, and IV, Branchial pockets; O, operculum; S, thyroid; spr, sinus præcervicalis; T, thymus; X, body derived from the fourth branchial pocket; oe, oesophagus.

work has shown that these have to do with the ganglia of the cranial nerves, and do not unite with the thymus as thought by His and others. Moreover, it is by no means probable that these sense organs of Froriep and Beard should suddenly leave the nerve ganglia in certain regions and unite with glands. Both observations and principles of development contradict this. The fourth branchial pocket, as well as a rudimentary fifth (fossa subbranchialis), gives rise to a few small bodies, the nature of which is not as yet truly known. That from the rudimentary fifth, no doubt, gives the gland which is homologous with Van Bemmelen's suprapericardial body.

In mammals the condition of things is much simpler (Fig. 5256). The branchial grooves lie on the outside of the body, are shallow on their dorsal side, and deep on their ventral. As these arches fall over one another, the grooves as well as the third and fourth arches are buried in the side of the neck; while this is taking place a pit is first formed, the sinus præcervicalis of His.

From the dorsal side of the first groove an invagination unites with the ganglion of the fifth nerve; from the second, the invagination is to the ninth nerve; and from the third and fourth it is to the tenth nerve. A section through these organs in the region of the vagus and of the thymus is shown in Fig. 5257. The ectodermal invagination is absolutely blended with the vagus and is only in apposition with the thymus.

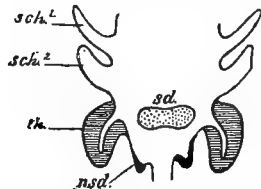


FIG. 5256.—Diagram showing Branchial Pockets, and the Glands arising from them in the Human Embryo. *sch¹*, *sch²*, First and second branchial pockets; *th*, thymus; *sd*, thyroid; *nsd*, lateral thyroid.

this region due to the rotation of the head. The first branchial pocket is converted directly into the Eustachian tube; the second disappears completely; the third forms the thymus (Fig. 5258); and the fourth becomes rudimentary and gives rise to the auxiliary thyroid glands.

The general appearance in the human embryo is quite similar to that in other mammals, as Fig. 5259 shows. Already in this early stage of development, the third branchial pocket shows an ingrowth which indicates the origin of the thymus. The portion of the cleft represented by the fundus (*F*) is not continuous with the thymus tube, and no doubt never plays any part in its formation.

The general view of the branchial pockets in a human embryo is shown in Fig. 5260. The whole pharynx is represented as a cast and the branchial pockets are rep-

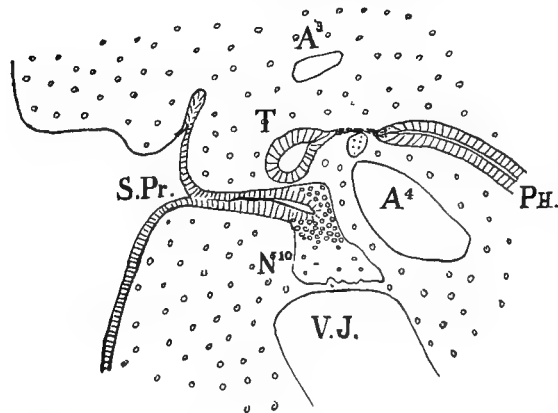


FIG. 5257.—Section through the Thymus and Fundus Præcervicalis of a Dog's Embryo, 10 mm. long. $\times 80$. *Ph.*, Pharynx; *A³*, *A⁴*, aortic arches; *S.Pr.*, sinus præcervicalis; *V.J.*, jugular vein; *T.*, thymus still in connection with the pharynx.

soon becomes separated from the pharynx and then grows into the thorax.

Before the thymus is separated from the pharynx it contains a distinct lumen. This is soon lost in birds,

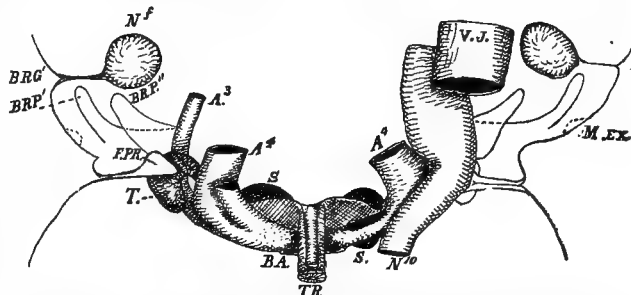


FIG. 5258.—Dorsal Reconstruction of the Branchial Region of a Dog's Embryo, 10 mm. long. $\times 25$. *N¹*, *N¹⁰*, Ganglia of facial and vagus nerves; *BRP¹*, *BRP²*, branchial pockets; *BRG*, branchial grooves; *A³*, *A⁴*, aortic arches; *BA*, aortic bulb; *Tr.*, trachea; *M.Ex.*, external meatus of the ear; *S*, thyroid; *T*, thymus; *F.P.R.*, fundus præcervicalis.

where the thymus grows toward the head. In mammals, where the thymus grows into the thorax, the upper part contains a lumen, while the lower part grows by a mass of sprouts (Fig. 5261). This continues for quite a while until the whole organ is lobulated. New blood-vessels and lymph cells grow through the epithelial gland and change its nature. The endodermal cells become packed together into the Hassal's concentric bodies as shown by Maurer for the fishes, and by Ecker²⁵ and by His²⁶ for mammals. These bodies correspond with the "pearls" in carcinomata, which are present in cancers, that arise from the whole epidermis, as well as those from the oesophagus. The Hassal's bodies do not therefore indicate that the thymus arises from the ectoderm.

During the first two years of life the organ continues to grow and the two halves gradually approach each other more and more, until they seem as a single body. It now lies immediately in front of the heart, and often

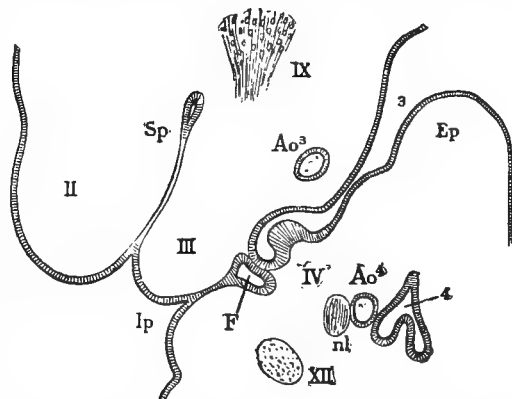


FIG. 5259.—Section through the Branchial Region of a Human Embryo, Five Weeks Old. (From Minot, after His.) *II*, *III*, *IV*, Branchial arches; *Sp*, second branchial grooves; *Ip*, infundibulum præcervicale; *F*, fundus of the infundibulum; *3*, *4*, third and fourth branchial pockets, with the thymus arising from the third; *A³*, *A⁴*, aortic arches; *Ep*, epiglottis; *IX*, glosso-pharyngeal nerve ganglion; *XII*, hypoglossal nerve; *nl*, superior laryngeal nerve.

sends two horns which extend on either side of the neck to the thyroid, as is the case in the birds. From now on, the organ gradually atrophies.

In the study of the human embryo Sudler²⁷ finds no indication of the thymus in a human embryo of the second week, but in one of the fourth week the third visceral pouch appears as a ridge with a ventral free end, with no differentiation of tissue to suggest a thymus. In

resented by the figures 1, 2, 3, and 4. It is the one marked 3 which is destined to become the thymus. It

an embryo four and one-half weeks old this ridge has disappeared and the third visceral pouch projects out

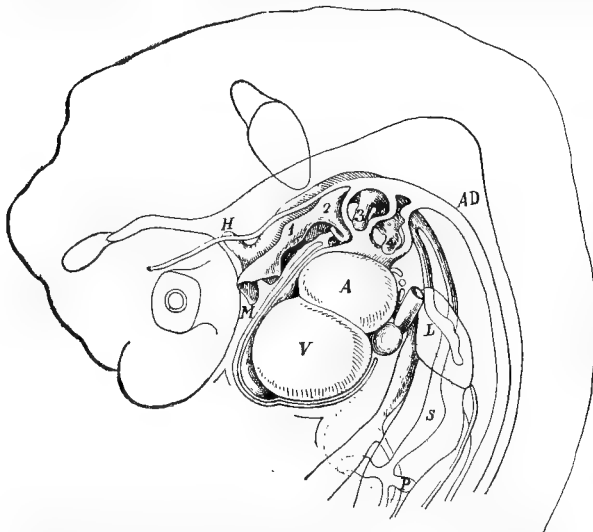


FIG. 5200.—Reconstruction of a Human Embryo Four Weeks Old. (No. 2.) Enlarged sixteen times, and viewed from the left side. *H*, Hypophysis; 1, 2, 3, and 4, branchial pockets; *M*, mouth; *A*, auricle; *V*, ventricle; *AD*, descending aorta; *L*, lung; *S*, stomach; *P*, pancreas.

directly from the pharynx (Fig. 5262). In the next stage, of about five weeks, it is very similar to one described by Born, in which the thymus has become completely separated from the pharynx, and its original hollow is reduced to a crescent-shaped opening which is quite characteristic of the gland at this stage. The thymus now is a curved elongated body with an enlarged cephalic end. The lower end of this and the thyroid (Fig. 5263) run parallel, though without coming in contact with each other till the thyroid bends abruptly and crosses the middle line. An embryo slightly older shows practically the same conditions, the differences being that the enlarged head is relatively smaller and the general curve of the thymus is less. A small process projects dorsally and laterally.

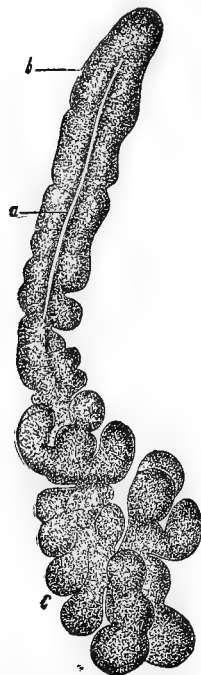


FIG. 5261.—Thymus of a Rabbit Embryo Sixteen Days Old. (After von Kölliker.) *a*, Duct of the thymus; *b*, head of the thymus; *c*, posterior enlargement of the gland.

lower. It is in contact with the thyroid along half of its upper surface, the lower end being free. In this free half the thymus and the thyroid approach each other

and meet in the middle line where the ends are slightly swollen and bend ventrally. This appears to be a beginning of the folding of the thymus found in the adult organ. In this embryo the thymus shows the same



FIG. 5262.—Lateral View of a Human Embryo Four and One-half Weeks Old (No. 163). Enlarged ten times. (After Sudler.) *Hy*, Hypophysis; *Oe*, oesophagus; *Thyr.m.*, median thyroid rudiment; *Tr*, trachea; *V.P.*—*V.P.v.*, first to fourth visceral pouches.

lack of bilateral symmetry which is apparent in the development of the pharynx in the human embryo as

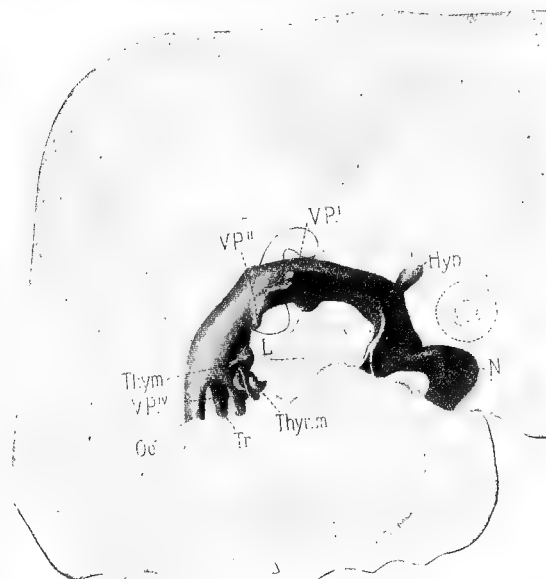


FIG. 5263.—Lateral View of the Pharynx of a Human Embryo Five Weeks Old (No. 109). Enlarged ten times. (After Sudler.) *N*, Nose; *L*, larynx; *Tr*, trachea; *Thym*, thymus; *Thyr.m.*, median thyroid; *V.P.*—*V.P.v.*, first to fourth visceral pouches.

well as that of some other animals. In this the rudiment extends a little higher on the right side than on the left.

From the study of these embryos it is apparent that in man the rudiment of the thymus arises from the entoderm of the third visceral pouch.

Franklin P. Mall.

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THYROID GLAND, DEVELOPMENT OF.—Shortly after Rathke discovered the branchial arches in higher animals, Huschke¹ advanced

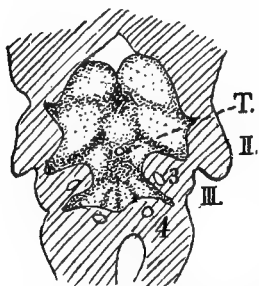


FIG. 5264.—Reconstruction of the Mouth of a Chick Eighty-eight Hours Old. The floor of the mouth is exposed by cutting off the back of the head. Dorsal view. X 20. T, Tuberculum impar, back of which is the opening of the thyroid; II, III, branchial arches; 3, 4, third and fourth aortic arches.

others in embryology, he was the first to give accurate information. He found that the thyroid is endodermal in origin and arises from the ventral median line of the pharynx. At first it appears as a single vesicle, which soon divides into two parts, each half lying on either side of the trachea. Götte,⁷ Müller,⁸ and Seessel⁹ confirmed Remak's views in general, differing only in minor points. They discussed whether or not the organ divided is a vesicle or is a solid body, although none of them found stages in which the thyroid was dividing. Remak placed the origin of the thyroid at seventy-nine hours in the chick; Müller in the third day; and Seessel very definitely in the second day before the head flexed upon the body.

His¹⁰ revived the old view of Rathke by discovering that certain bodies arise from either side of the pharynx; he believed them to be the thyroid and the auxiliary thyroid of Remak. According to the illustrations which accompany his paper, the gland arises from the branchial cleft between the second and third aortic arches, therefore the second cleft. Later, however, he abandoned this view and accepted that of Seessel, who worked under his guidance. Later, Kölliker¹¹ accepted the old Remak-Seessel view for the rabbit, as His¹² did for man.

This group of excellent workers seemed to set the subject aside for a while, but, immediately following their work, two authors simultaneously described the thyroid as being bilateral in origin, arising from a branchial cleft

on either side of the neck. Stieda¹³ proved definitely that a glandular organ arises from the clefts on either side of the neck, but did not know from which cleft, although he was inclined to accept the fourth. Wölfler¹⁴

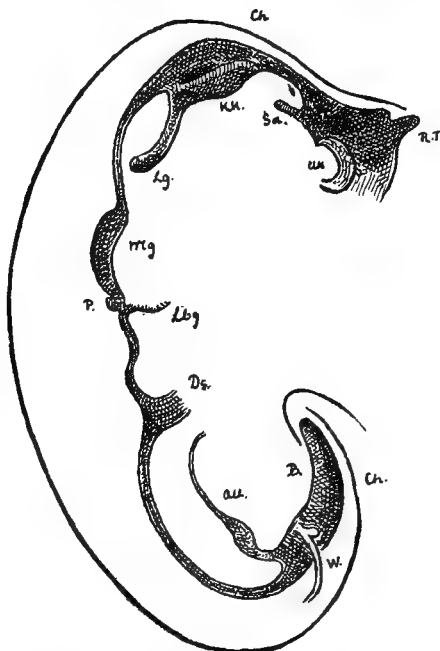


FIG. 5265.—Alimentary Canal of a Human Embryo. X 20. (After His.) Uk, Lower jaw; Sd., thyroid; Lg., lung; Mg., stomach; P., pancreas; Lbg., bile duct; W., Wolffian duct.

did not employ very accurate methods, and therefore got the location of the origin of the gland in the first branchial cleft—the one which later forms the Eustachian tube. He was so enthusiastic over his discovery that he denied altogether a median thyroid, although he had never seen the thyroid in connection with any cleft. Discussions naturally bring forth more accurate investigations, and in this case they bore their fruits in Born's paper.¹⁵ The paper of Born not only threw a great deal of light upon the subject in question, but also added

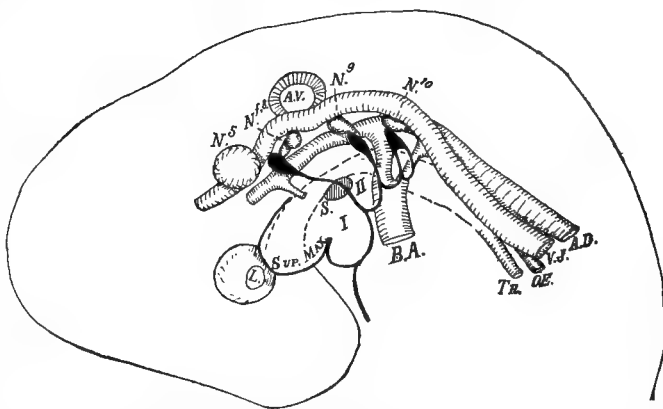


FIG. 5266.—Profile Reconstruction of a Dog's Embryo, 6 mm. long. X 25. N's, Nf's, N's, N's, ganglia or cranial nerves; I, II, branchial arches; AV., auditory vesicle; Tr., trachea; OE., oesophagus; V.J., jugular vein; A.D., descending aorta; B.A., bulbus aortae; S., thyroid gland.

greatly to our methods of investigation. He introduced a method which to us now seems so logical that it is a surprise that it was not employed earlier. He began with embryos of the pig before the thyroid appeared, and

followed them stage by stage until the organ was fully formed. In each stage the enlarged sections were drawn upon wax plates of the proper thickness, then cut out and the pieces piled upon one another, thus forming very accurate models of the various specimens studied. He then followed the lateral thyroids of Stieda and Wölfler, and found that later on they were added to the median thyroid of Remak. The great difficulty was therefore solved by this method. Instead of these various authors contradicting one another, they in reality described correctly only different portions of the same story. According to Born the lateral thyroids arise from the fourth branchial clefts. Since then, Born's view has been confirmed in a variety of mammalian embryos by different writers¹⁶⁻²⁵

The subject of the origin of the thyroid and thymus (see *Thymus*) has been greatly complicated by a group of glands which arise from the degenerating branchial clefts and form the so-called auxiliary thyroid glands. From a phylogenetic standpoint all glands which arise from the clefts must be viewed as thymus. The great bulk of thyroid arises from the ventral wall of the pharynx in the region of the second cleft. As the clefts gradually disappear in the evolution of the vertebrates, the glands from the hindermost clefts no longer unite with the main bulk of the thymus, and often remain as distinct glands—the suprapericardial bodies of van Bemmelen, accessory thyroids of de Meuron, post-branchial body of Maurer, or as the corpus Y of the writer.²⁶ In the mammals the main bulk of the thymus arises from the third cleft, and the auxiliary thyroids seem to unite with the median thyroid as described by Born. In spite of the great amount of work which has been done upon this subject, it still seems to the writer that there is yet considerable darkness regarding it.

The general view is that the thyroid has three distinct origins in nearly all vertebrates—a median and two lateral. The median arises from the ectoderm of the middle line in the neighborhood of the second branchial arch (Fig. 5264), and the lateral from the most posterior branchial clefts; in mammals, the fourth.

The median thyroid arises in all vertebrates from the entoderm of the pharynx shortly after the branchial arches are well formed (Fig. 5265). This has been known since the time of W. Müller, and, although contradicted many a time, has of late been verified by so many careful observers that there is no longer any doubt whatever regarding it. In some mammals (the dog, for instance) it arises as a vesicle, which becomes solid before it separates from the pharynx, and when separated soon becomes lobulated. It now gradually shifts itself into the tissue of the neck, and in early stages lies in front of the aorta just as it leaves the heart (Fig. 5266). The median gland now becomes constricted into two parts, one of which is situated on either side of the neck, but they remain connected by a band—the isthmus. Its origin in the human embryo is much the same (Figs. 5267

ever, the formation of the ligamentum hypothyroideum cuts the duct (*d. thyreoglossus*) into two, thus forming two ducts. The half communicating with the mouth has been termed by His *ductus lingualis*, and the one with

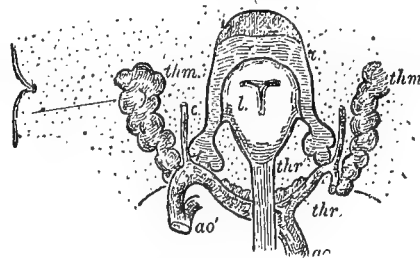


FIG. 5268.—Reconstruction of the Thyroid, Thymus, and Pharynx of a Human Embryo Five Weeks Old. (Slightly modified from His.) *thm.*, Thymus; *thr.*, thyroid; *c.*, carotid; *ao'*, ascending aorta; *ao*, descending aorta; *tr.*, trachea.

the thyroid as the *ductus thyroideus*. His has found the *ductus lingualis* in five adults, and in all cases the *ductus thyroideus* was present also. The latter is always embedded in a median lobe of the thyroid, and the former opens into the foramen cæcum of the tongue. The *ductus thyreoglossus* may be broken into a series of vesicles, as first described by Verneuil, but as a rule it disappears fully, its only remnant being the foramen cæcum.*

The lateral thyroids were first demonstrated by Stieda and by Born, although Rathke, His, and others had in all

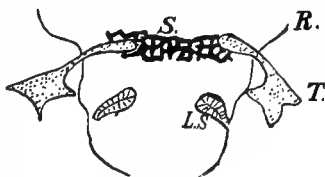


FIG. 5269.

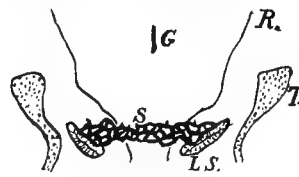


FIG. 5270.

FIGS. 5269 AND 5270.—Diagrams of Two Stages of the Development of the Lateral Thyroids. (Slightly modified from Born.) *R.*, Border of the pharynx; *T.*, thymus; *G.*, glottis; *L.S.*, lateral thyroids.

probability described them from time to time. The true meaning of them was fully made out by Born and by de Meuron, the former having discovered that they unite with the median thyroid in mammals, the latter having studied them from a comparative standpoint. Diagrams of the branchial pockets for some of the different classes of vertebrates are given in the article *Thymus*, and by them it is shown that a rudimentary branchial pocket exists in all of the classes. In certain reptiles there is but a single one on the left side, the one on the right not having developed. We can view this state of things only as an intermediate one between the reptiles (in which they develop on both sides) and the birds. In all classes the hindermost cleft gives rise to a distinct gland known as the suprapericardial body of van Bemmelen and as the accessory thyroid of de Meuron.²⁸⁻³⁰ In the selacians these bodies remain far away from the median thyroid, and they never unite with it. In higher animals they gradually approach the median thyroid nearer and nearer, and in mammals they unite completely with it. Fig. 5268 shows the general relation of these glands in a human embryo before the lateral thyroid is fully separated from the pharynx. Figs. 5269 and 5270 show two stages in which the lateral thyroid is approaching and uniting with the median. This is brought about by a

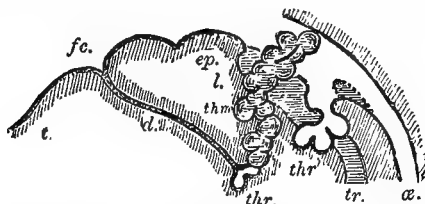


FIG. 5267.—Pharynx, Thyroid, and Thymus of a Human Embryo, $\times 25$. (From Quain, after His.) *tr.*, Tongue; *fc.*, foramen cæcum; *ep.*, epiglottis; *thm.*, thymus; *thr.*, median thyroid; *thr'*, lateral thyroid; *d.*, ductus thyreoglossus.

and 5268). According to His, it remains a vesicle for quite a long time, and the separation from the pharynx occurs quite late or may not take place at all. Later, how-

* From the standpoint of evolution it is interesting to note that Dohrn²⁷ has advanced the hypothesis that the thyroid represents a lost branchial cleft. These speculations are, of course, the natural outcome when genetic relation is taken into consideration in the study of comparative embryology.

double shifting. The median thyroid sinks deeper and deeper into the tissue of the neck, and practically lies in contact with the lateral thyroids before they separate from the pharynx. When these in turn separate from the pharynx they are shoved into the tissue of the median thyroid instead of into the ordinary mesoderm tissue of the neck.

It will be noticed that the lateral thyroids do not always arise from the same branchial clefts: in selacians from the seventh; in reptiles from the fifth; in mammals from the fourth. It is only in mammals that they really unite with the median thyroid. Viewing the thing from the standpoint of homology, what is lateral thyroid in mammals is thymus in lower animals; in both selacians and reptiles the fourth cleft gives rise to a portion of the thymus. We must therefore view the lateral thyroid as a portion of the thymus which is now united with the thyroid. In lower animals the secondary union of the gland from degenerating clefts with the median thyroid does not take place, and they remain in the tissue of the neck, as in the auxiliary thyroid glands, which have perplexed so many investigators. According to Kastschenko the lateral thyroid of mammals plays a very minor part in the formation of the mature organ, while according to His it forms the major part. A true blending of the two does, however, take place, as shown by the investigations of Born and of His (Fig. 5271).

The further development of the thyroid is by means of sprouting, so that the enlarged organ is a plexiform mass of cylinders of epithelial cells. Blood-vessels grow in between them, and soon the cylinders show constrictions which cut them up again and again. They now become hollow, and at the same time there is a secretion of the colloid substance. The cut-up cylinders become more and more distended, and thus the adult thyroid is composed of a mass of hollow spheres covered with a layer of epithelial cells and filled with colloid substance. When half of the thyroid is removed by an operation or otherwise, the remaining portion soon loses its colloid and returns to its "embryonic state." It enlarges to its former size and again forms the colloid spheres much after the fashion it did in the embryo.³¹

In the human embryo Sudler³² finds the thyroid rudiment in the earliest one studied, an embryo at the end of the second week. It appears as a rounded eminence on the ridges uniting the first pair of visceral pouches. Its outline is elliptical, being broader from side to side than it is ventrodorsally. This is the rudiment of both the thyroid gland and the ductus thyreoglossus.

In an embryo of the fourth week the rudiment appears as a solid body extending dorsally from the apex of the

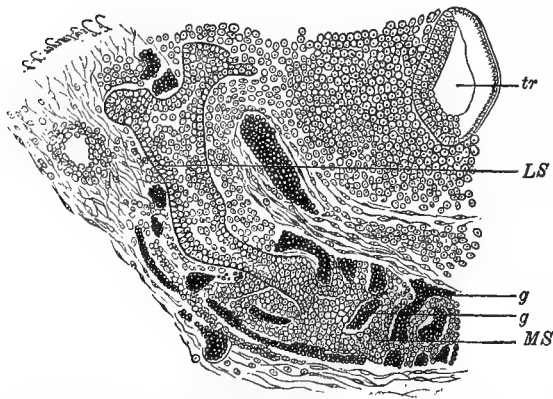


FIG. 5271.—Section through the Thyroid of the Embryo of the Fig. 21.5 mm. long. x 80. (From Hertwig, after Born.) tr, Trachea; LS., lateral thyroid; MS, median thyroid; g, g, blood-vessels.

angle formed by the meeting of the first visceral pouches (Fig. 5272). Just oral to it is the hollow cavity representing the inner of the second visceral arches and direct-

ly aboral is the hollow cavity representing the tuberculum impar. Its appearance is that of a knob on a short slender stem. The fourth visceral pouch at this stage shows no thickening or development into the lateral thyroid rudiment.

In an embryo of four and one-half weeks the thyreoglossal duct remains as a small conical eminence on the

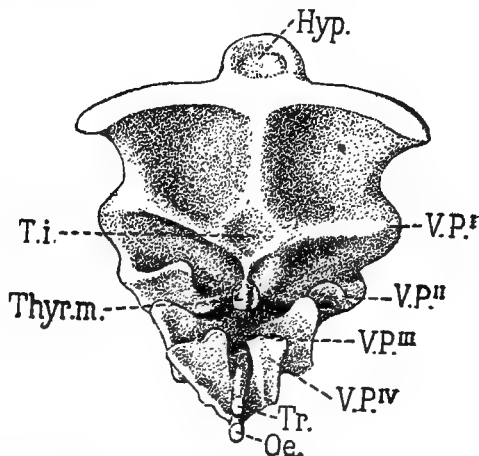


FIG. 5272.—Ventral View of a Model of the Pharynx of an Embryo Four Weeks Old (No. 2). (After Sudler.) Hyp., Hypophysis; Oe., oesophagus; T.i., depression of the tuberculum impar; Thyr.m., median thyroid rudiment; Tr., trachea; VP-I-VP-IV, first to fourth visceral pouches.

ridge connecting the first visceral pouches. It is at the junction of the tuberculum impar and the two dorsal rudiments of the tongue (Fig. 5273). The median thyroid rudiment has become entirely disconnected and has sunk to the level of the third visceral fold. It has spread out laterally and has a bilobed structure. The left lobe

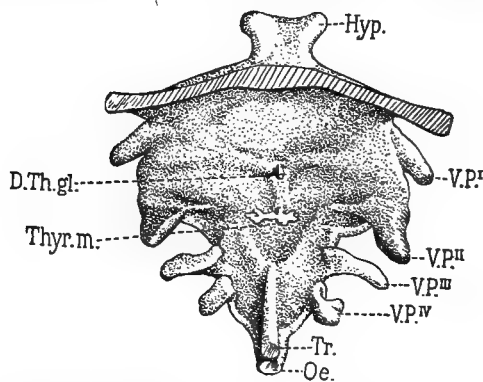


FIG. 5273.—Ventral View of a Model of the Pharynx of an Embryo Four and One-half Weeks Old (No. 183). (After Sudler.) D.Th.gl., ductus thyreoglossus.

is much the longer and approaches closer to the floor of the mouth than the right. In this the fourth visceral pouches appear as two ventral projections with enlarged knobs bent sharply dorsal.

In an embryo of five weeks the median thyroid rudiment has become U-shaped, though the left arm is much longer than the right (Fig. 5274). Its outline is quite irregular. In this the transverse part of the U which runs across the middle line has sunk to the level of the fourth visceral pouch. This part shows the usual network structure formed by cords of solid cells. The arms are crescentic in cross section, with the hollow looking away from the middle line and embracing the thymus, although the two do not come in contact. The lateral thyroid rudiments, which consist of hollow tubes surmounted by solid expansions, are still connected with the

pharynx. The two sides are unsymmetrical. On the right side the ventral knob is smaller than the dorsal, while on the left they are about equal in size and placed on the same level.

In an embryo only slightly older the median thyroid is still U-shaped, though the right arm is still smaller than

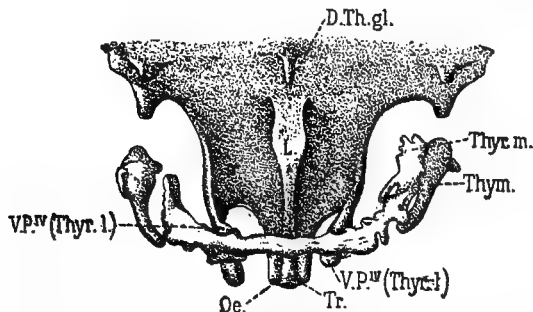


FIG. 5274.—Ventral View of the Pharynx of an Embryo Five Weeks Old (No. 109). (After Sudler.)

in the last and not so long as the one on the left side. The lateral rudiments show in this embryo the greatest lack of symmetry of any of those studied by Sudler (Fig. 5275). The right rudiment is still connected with the pharynx by a small hollow stalk, while on the left side this connection has entirely disappeared. On the right side the ventral knob touches the middle of the right arm of the median rudiment, but there is no histological continuity, whereas on the left side the ventral knob not only touches the median rudiment, but there is actual continuity. As in the embryo described before, the ventral knob on the right side is much smaller than the dorsal one, while on the left side they are of almost the same size.

The median and lateral thyroid rudiments have united on both sides in an embryo of the sixth week, and all connection with the pharynx has disappeared. They still appear as distinct rudiments.

In a slightly older stage the lateral rudiments and the median have so completely united that all there is to show that they were once separate are a few prominent lobules at their point of union. The loop of the U has become smaller and the arms larger, and they have become lobulated, so approaching the condition of the adult gland.

In the last embryo studied, one of the seventh week, the shape is almost that of the adult thyroid. The two lateral lobes are pyriform and are connected by a small isthmus, which is attached to them at the smaller end.

In the human embryo, as well as in the bird and some of the mammals, the pharynx develops more slowly on the right side than on the left, and the most striking example of this is in the thyroid. This may be due to the development of the heart and the bending of the head to the left.

From these different embryos Sudler draws the conclusion that "the thyroid arises in the human embryo from the union of a median rudiment situated at the point of junction of the tuberculum impar and the two

dorsal rudiments of the tongue with a paired rudiment arising as a differentiation of a lining of the fourth visceral pouch."

Franklin P. Mall.

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TICK FEVER, OR SPOTTED FEVER.—A disease known by the latter of these two names is found in the States of Montana, Idaho, Nevada, Wyoming, and Oregon. As two other diseases (viz., typhus fever and cerebro-spinal meningitis) are already known as spotted fever, it would be well, as suggested by Anderson, to call the disease under discussion tick fever.

ETIOLOGY.—Tick fever or spotted fever is found in the mountainous districts in the above-named States at an elevation of over three thousand feet. It does not seem to be prevalent outside the latitude of 40° to 47° N. The disease is only found in persons whose occupation causes them to be exposed to the bite of the tick; such are lumbermen, ranchmen, and sheep-herders. Males in the prime of life are most liable to the disease; this would be expected from the occupations just mentioned. Beyond this, age and sex have no etiological significance. The disease is in all probability caused by a parasite.

The Parasite.—"Wilson and Chowning noticed ovoid intracorporeal bodies in stained preparations of the blood from their earlier cases. They did not determine the character or significance of these bodies until they examined the fresh blood, when they found ovoid intracorporeal bodies showing amœboid movements. These observations they confirmed in all the later cases which they examined. To Wilson and Chowning, then, belongs the credit of discovering a parasite which is very probably the cause of spotted (tick) fever." Anderson further says that in his studies upon the cause of this disease he "had the opportunity of examining the blood, both fresh and stained, in a number of cases. Two cases were in a hospital in Missoula, and daily examinations were made. In the fresh blood a few cells were found to contain parasites. Three forms were seen. The most common was a single ovoid body, refractile, situated within the cell, usually near its edge. When the slide is warmed this body possesses the power of projecting quite rapidly pseudopodia and of effecting a slight change of position. This form, which is apparently an early or young form, is about 1.5–2 μ in length, and 0.5–1 μ in width at its widest part. It closely resembles the earliest intracorporeal parasites of æstivo-autumnal malaria.

"Another form, not so common, was larger, being about 2–2.5 by 1–1.5 μ , larger at one end and showing in the larger end a dark granular spot; this was also amœboid.

"The third form noted was arranged in pairs, distinctly pyriform, with the smaller ends approaching, and in two cases a fine thread uniting the small ends was seen. Motion was not observed in this form, but the spot mentioned in the second form was seen.

"The parasites are never found in very large numbers, it being usually necessary to search several fields of the slide to find one. Sometimes they occur in groups, two or three infected cells being found in one field. In both fresh and stained preparations extracorporeal bodies closely resembling the small single intracorporeal form were seen. I was unable definitely to decide the character of these bodies, but am strongly inclined to think that they are the young form of the parasite which has not yet invaded the red cells.

"In the cases of spotted (tick) fever which I had the opportunity of examining I had no great difficulty in finding both in fresh and in stained preparations the bodies above described. Their constancy in the blood of persons suffering with spotted fever, their persistence for some time in the blood of these persons after recovery, their absence from the blood of persons suffering from other diseases and of healthy persons make it very probable that they are the cause of the disease, and that one more has been added to the rapidly growing list of diseases of man due to animal parasites." (Anderson: "Spotted Fever (Tick Fever) of the Rocky Mountains.")

Method of Infection.—"The life history of the organisms of malaria and Texas fever naturally suggested that some insect was concerned in the transmission of the disease. On investigation it was found that the ticks appeared in the valley about the last of February, but were inactive until the middle of March or 1st of April, the first cases of fever appearing about the last of March. The ticks begin to diminish greatly in number from about June 1st, and after the middle of July very few are seen; the cases of fever also begin to diminish about June 1st, the latest date on which the disease has been known to occur being July 20th.

"Mosquitoes do not appear in the valley until after the first cases of fever develop, and remain some time after the last cases appear. Bedbugs and other house insects, I think, were well excluded, by the fact that there has never been known an instance in which two cases occurred the same year in the same house.

"On a closer study of the cases of spotted (tick) fever it was always found that there was a history of tick bites about one week before the onset. In four cases there was a history of a single bite two, three, five, and seven days, respectively, before the initial symptoms. The usual time between the bite and the onset of the fever is about seven days. If the tick transmits the disease, it may be asked, Why do not more persons become infected, and why is the infection confined to the west bank of the Bitter Root River? I think this may be answered by the very obvious fact that the tick is unable to travel any great distance, unless carried on some person or object. Again, it is very unusual for a tick to bite a person and not be discovered in a short while, and the result is the death of the tick. If, as in Texas fever, the development of the parasite takes place in the female tick and the young ticks transmit the infection, the very small number of ticks which escape detection in persons explains the small number of infected ticks. Where do the female ticks get their infection? I examined a recovered case twenty-four days after discharge by the physician and had no trouble in finding the parasite in the fresh blood. This child had been out of doors for over two weeks, and if a female tick (ticks were quite numerous near the house) had bitten her and escaped destruction the parasites in the blood taken in by the tick would have undergone development, and the young ticks, when hatched out, would be ready to infect prospective victims.

"While the above facts and conclusions tend strongly to the belief that the ticks are necessary for the transmission of the disease, the actual fact cannot be proved scientifically until carefully controlled experiments are made on non-immune persons." (Anderson, *ut supra*.)

The tick in question is in all probability *Dermacentor reticulatus*.

MORBID ANATOMY.—Rigor mortis is intense, and appears early. The skin is jaundiced, has a mottled appearance, and the wounds caused by the tick bites may be present. Petechial spots, bright to dark purple in color, and from 1 to 3 cm. in diameter, are found, chiefly on the wrist, ankle, arm, and leg. The spleen, liver, and pancreas are much enlarged; the kidneys are also enlarged.

SYMPTOMS.—There is a period of incubation of about a week. The patient complains of nausea, general malaise, and a chill; this latter is followed by a fever which reaches its highest point about the tenth day, is characterized by evening rise and morning remissions, lasts about two weeks, and may be followed by subnormal temperature. In severe cases the morning remissions may be absent, and the fever remains high (from 104° to 106° F.). There are general pain and soreness, particularly during the first week, coated tongue with red edges, sordes, constipation, nausea which persists in severe cases, scanty urine with albumin and casts, and epistaxis. The liver and spleen may be enlarged. The pulse is high, and out of all proportion to the fever; the respiration is also increased. An examination of the blood shows: (1) the parasite described above; (2) a decrease in the percentage of hemoglobin; (3) a decrease in the number of the red blood cells; (4) a slight leucocytosis, chiefly of the large mononuclears. Bronchitis is present during the second week; and in severe cases lobar pneumonia supervenes, with a grave prognosis.

"The eruption appears usually on the third day, first on the wrists and ankles, then on arms, legs, forehead, back, chest, and, last and least, on the abdomen. It is never very abundant on the abdomen, but the other portions of the body, in some cases, are literally covered by the eruption.

"At first the spots are of a bright red color, macular at all times, from a pin point to a split pea in size. At first they disappear readily on pressure and return quickly, but if the case is a severe one they soon become darker and in some cases are almost purple. From about the sixth to the tenth day of the disease they fail to disappear on pressure and are distinctly petechial in character. In favorable cases, about the fourteenth day, they begin to lose their petechial character and disappear slowly on pressure. In some cases the eruption consists of small, brownish spots, giving a turkey-egg appearance.

"As the fever declines the eruption begins to fade; but a slight return of fever or a free perspiration will cause it to show distinctly.

"When convalescence is well advanced desquamation begins and extends over the entire body. In very severe cases there may be gangrene of the fingers or toes, and still more frequently of the skin of the scrotum and penis. The skin is always jaundiced to a greater or less degree. This is usually first noticed in the conjunctivæ, the vessels of which are congested from the outset." (Anderson, *ut supra*.)

	Tick fever or spotted fever.	Typhoid fever.	Typhus fever.
Contagion ...	Non-contagious ..	Not contagious in the ordinary acceptance of the term.	Very contagious.
Geographical distribution.	From 40° to 47° N.	Universal	Almost universal.
Season	March to July....	All the year; chiefly July to November.	Generally in the winter.
Eruption—Date of occurrence.	Third day.....	Second week.....	Third to fifth day.
Site of first appearance.	Wrists and ankles, arms and legs.	Abdomen and back.	Abdomen, flexor surfaces of forearms, and general, except on face.
Blood examination.	Shows parasite...	Eberth's bacillus in cultures from blood. Widal reaction.	Negative.

DIAGNOSIS.—This is made from: (1) The case occurring in the region known to be infected; (2) history of a tick bite; (3) the eruption appearing on the third day, and being seen first on the wrist and ankles; and (4) the presence of the parasite in the blood. The diseases from which it is to be differentiated are typhoid fever and typhus fever, particularly the latter. The preceding table will assist in making a diagnosis.

PROGNOSIS.—This is unfavorable. Up to the present the death rate from tick fever has been seventy to ninety per cent. in Montana; but in Idaho and Nevada it is much lower. The disease varies in malignancy both in different localities and in different years in the same locality.

TREATMENT.—The treatment has so far been unsatisfactory; but in five cases, all treated by quinine, all recovered. Anderson suggests the bimuriate of quinine, 1 gm. (gr. xvi.) hypodermatically, q. 6. h.; or, by mouth, the sulphate of quinine in similar doses, q. 4. h. This drug should be given persistently from the commencement of the disease. The treatment is otherwise symptomatic, and includes cardiac stimulants, Dover's powder for the pains and soreness, tepid baths for the fever, and plenty of water to flush out the kidneys. The site of the tick bite should be cauterized with ninety-five-per-cent. carbolic acid.

R. J. E. Scott.

REFERENCE.

Anderson, John F.: Spotted Fever (Tick Fever) of the Rocky Mountains. Bull. No. 14, Hyg. Lab., U. S. Pub. Health and Marine-Hospital Service, Washington, p. 50. From this pamphlet, which gives all that is known of spotted, or tick fever, the above article has been compiled.

TUBERCULOSIS, INTESTINES AS A PORTAL OF ENTRANCE OF THE BACILLI OF.

—There can be no doubt that the intestines are one of the portals of entrance for the tubercle bacillus. Particularly in the case of young children is tuberculous infection through the alimentary tract of not infrequent occurrence. Both experimental and pathological evidence has been presented to prove conclusively that tubercle bacilli may pass through the intestinal mucosa without exciting local lesions, and, entering the lymph stream, be carried through the thoracic duct into the blood, which conveys them to the lungs, where they are either wholly or for the greater part dropped out of the circulation to excite first in this organ the local lesions of the infection. Since the facts of such an avenue of tuberculous infection have been indubitably established, the questions of importance relative to this subject are those concerned with the source and character of the tubercle bacilli gaining entrance into the intestines, the conditions under which they pass through the intestinal wall, and the relative frequency of such an occurrence. Great interest has centred around these questions during the last several years, and the experimental investigations and pathological studies resulting therefrom have greatly modified some of our former views concerning the nature and mode of tuberculous infection.

The belief that tuberculosis can be acquired through the alimentary tract is, of course, not a new one. As early as 1846 Klenke pointed out the possibility of such an infection in children fed with cow's milk. Experimental proof of an alimentary infection of tuberculosis was first offered by Chauveau (1868) and Villemin (1869), and confirmed later by Gerlach, Günther and Harms, Klebs, Bollinger, Orth, Baumgarten, and numerous others. All of these investigators showed that in experimental animals a tuberculous infection could be readily induced through the alimentary tract. Practical confirmation of the experimental work through investigations as to the spread of tuberculosis among the domestic animals was soon forthcoming; and the demonstration of tubercle bacilli in cow's milk and its products made clear the possibility of human infection through such sources. A belief in the important part played by cow's milk was therefore aroused and was beginning to play an important rôle in clinical and sanitary matters when Koch at the International Congress

in 1901 took ground against the doctrine and announced his dictum that human and bovine tuberculosis were different in kind, and that there was but little danger of human beings becoming infected through the food and by way of the intestine.

A storm of discussion followed Koch's statement, and much of the work concerning tuberculosis in the six years since it was made has been concerned with its refutation. This may be said to have been completely accomplished, and incidentally we have made much progress in our knowledge of tuberculosis. The pendulum of opinion, however, has swung much farther in the other direction than was at first imagined, for certain workers have gone so far as to cast doubt upon the occurrence of aerogenous tuberculosis and to refer the majority, if not all, of the cases of pulmonary tuberculosis to infection received through the intestine. Nevertheless, a few investigators, notably Ribbert, oppose the modern view of the intestines as a portal of tuberculous infection and uphold the old belief of a primary airborne infection of the lungs. The majority of writers upon tuberculosis accept the middle ground between these extremes of opinion. They recognize the occurrence of bovine tuberculosis in human beings, acknowledge the intestines as the portal of infection, and cow's milk as the conveyor of the bacilli, and emphasize the practical importance of these facts in their relation to infant-feeding and the occurrence of tuberculosis in young individuals. On the other hand, they do not deny the occurrence of air-borne infections, nor do they underrate their importance.

The refutation of Koch's statement rested upon the establishment of the permeability of the intestinal wall by tubercle bacilli without the production of tuberculous lesions in the wall, as well as upon the proof of the infection of human beings by bovine bacilli. The chief argument used by Koch in support of his statement was to the effect that a food infection of tuberculosis could be assumed to have occurred only when a primary tuberculous lesion was present in the intestines. Since primary intestinal tuberculosis is relatively rare, he affirmed that the chances of infection through the food must be likewise slight.

Recent statistics concerning primary intestinal tuberculosis tend to show that it is much more frequent than was supposed. While pathologists and clinicians in different localities vary greatly in their reports as to the frequency of primary intestinal tuberculosis, numerous competent observers (Hueppe, Hof, Wagener, Heller, Lubarsch, et al.) have found it in from twenty to thirty per cent. of all cases of tuberculosis in children. Statistics constantly accumulate to show that it is not of infrequent occurrence in milk-fed children.

For the support of the doctrine of primary infection through the intestinal tract it is not, however, necessary to fall back upon the frequency of intestinal lesions, since the much more important fact has been established that tubercle bacilli may pass through the intestinal mucosa without exciting in it any tuberculous lesions. The passage of tubercle-bacilli through the uninjured intestinal mucosa was discovered by Orth in 1879, Cornet in 1880, and Dobrolonski in 1890. Desonfry and Porcher, Nicolas and Descos, Ravenel, von Behring, Bartel, Besanti and Panisset, and others have shown the passage of tubercle bacilli through the uninjured mucosa of the intestines of dogs and guinea-pigs during the process of digestion, particularly that of fats. When fat is absent from the food the number of bacilli passing through the wall has been shown to be much less than in the presence of fat.

The views of Calmette and his colleagues on the intestinal derivation of anthracosis and pulmonary tuberculosis have attracted wide-spread attention. They hold that animals breathing an atmosphere containing carbon do not develop anthracosis when the œsophagus is closed, but, on the other hand, anthracosis of the lungs is rapidly produced by the introduction of carbon into the stomach. In connection with these experiments

they found that tubercle bacilli introduced into the intestine readily pass through the wall into the chyle vessels, where they are taken up by leucocytes and carried to the mesenteric glands and thence through the thoracic duct into the circulation. Calmette's theory concerning the intestinal origin of anthracosis has been attacked by a number of other investigators who have been unable to confirm his results. The passage of tubercle bacilli through the uninjured intestinal wall has, however, been confirmed by so many investigators that we must accept the evidence. Such a passage has also been demonstrated for other bacteria, notably anthrax and glanders bacilli.

Other proof of the intestinal entrance of tubercle bacilli in the absence of intestinal lesions may be found in the not infrequent occurrence of primary tuberculosis of the mesenteric glands. A latent infection of the mesenteric glands by tubercle bacilli without the production of histological changes of tuberculosis has been positively demonstrated by Rabinowitsch and others. Primary infections of the liver through the portal veins in the absence of tuberculosis elsewhere in the body may also be taken as evidence favoring the intestine as the avenue of entrance. Some writers have suggested that in the cases of apparently primary mesenteric-gland tuberculosis there may have been a slight primary lesion in the intestinal mucosa that had healed, leaving no traces. Such a supposition is not at all necessary for the proof of intestinal infection.

That bovine tubercle bacilli are capable of infecting man has been abundantly proved. Ravenel, de Schweinitz, Mohler, Smith, Wolff, Westenhoffer, Febiger and Jensen, and others have isolated from human cases virulent bovine tubercle bacilli. The English Royal Commission examined sixty cases of human tuberculosis and found the bovine bacillus in fourteen cases (23 per cent.). Of the sixty cases twenty-eight possessed clinical histories indicating an intestinal infection. Thirteen of these cases were due to bovine infection. In nineteen cases of abdominal tuberculosis studied by this commission ten cases were shown to be of the bovine type; and in fifty-six cultures from man examined by the German Commission ten per cent. were found to be of the bovine type. Numerous cases of local bovine infections have been seen in butchers and veterinarians.

The possibility of human infection by bovine bacilli having once been demonstrated, it follows that the majority of such cases not due to local cutaneous infection must have been due to intestinal infection, since the possibility of an inhalation of bovine bacilli, particularly by young children, is so slight as practically to be disregarded. Milk or butter from tuberculous cows must be regarded as the chief, if not the only, source of these intestinal infections of early life in which the bovine bacilli are present.

The great question under discussion is the frequency of intestinal infection as compared with that due to inhalation, and the International Conferences of 1906 and 1907 were largely occupied with a discussion of this problem. Von Behring and Calmette represented the extreme point of view concerning the intestinal route of tuberculosis infections. The former reports his views with emphasis that ingestion is the most frequent and important method of infection, and that tuberculosis in the adult is a delayed development of a latent infantile intestinal infection. Calmette's views have been even more sensational. He insisted in 1906 that pulmonary infection always occurred through bacilli gaining entrance to the blood by way of the intestinal tract and lymph stream, supporting his view by his experimental work concerning the origin of anthracosis. The bacilli may be of the bovine type and enter the intestine through milk or its products, or they may be of the human strain, entering the body with dust and swallowed with the saliva. In 1907 he modified his views to the extent of admitting that an aërogenous pulmonary infection may occur but is relatively uncommon. He still asserts, however, that the chief danger of infec-

tion through dust lies in its being swallowed with the saliva. He warns against the danger of swallowing the saliva produced during exposure to a dusty atmosphere.

Weber (1906) in a special study of the bovine origin of human tuberculosis concluded that the *perlsucht* bacilli easily enter through the intestine or cervical glands in the case of children, but that such a form of infection is rare after the twentieth year. Human transference of the bovine bacilli is rare, hence in adult life tuberculous infection is almost wholly due to the human form. Raw (1907) practically agrees with this view. He divides all cases of tuberculosis into two classes, the bovine form due to a milk-borne intestinal infection, and the human form due to an inhalation infection. To the latter class belongs pulmonary tuberculosis, while in the former he would place all other forms of tuberculosis infection such as glandular, arthritic, etc., particularly when occurring in the young. Between the two types of bacilli he believes there is a mutual antagonism, as demonstrated by the successful treatment of one form by the tuberculin prepared from the other. Accordingly bovine infection in man must tend to cure or immunize those infected with human tubercle bacilli. Bovine immunization as advocated by Behring may be so developed as to offer a cure for the human infection, but this happy result has not yet been achieved and we must await the test of future experimentation. On the other hand, it has been pointed out by a number of writers that if bovine infections immunize against infections with human bacilli, the prevention of bovine tuberculosis through a perfect sanitary control of the milk supply might be expected to increase the susceptibility of many individuals to infection with the human strain. Numerous writers assert that, in spite of the great care taken in recent years to safeguard the milk supply, there is no corresponding diminution in the frequency of infantile tuberculosis. They consider this fact as a strong argument in favor of the aërogenous nature of the infection. Calmette answers this by pointing to the fact that infantile tuberculosis is usually localized in the tracheobronchial glands, and regards this localization as an evidence of an intestinal entrance and a lymphatic route, both for bovine bacilli ingested with the milk and human bacilli swallowed with the saliva.

Experimental proof of Calmette's views has been offered by Vallée. Calves were fed for a long time with the milk of cows infected through the administration of moderate quantities of bacilli. No udder lesions were produced, but the cows gave positive tuberculin reactions. In the calves so fed intrathoracic lesions developed without any apparent involvement of the mesenteric glands. These, however, gave positive results on inoculation. Similar results as to the path of the infective agent were obtained in guinea-pigs by Schlossmann and Engel. Injections of tubercle bacilli directly into the stomach were followed by the development of pulmonary lesions. On the other hand, other workers have failed to confirm experimentally the views of Calmette and his colleagues. Huss and Lobstein, Gaffky, Frosch, and others at the 1907 Congress favored inhalation as the more important method of infection in man. At the same time Weichselbaum and Orth expressed the opinion that we are not able at the present time to state which is the more common mode of infection. In an address delivered before the XIV. International Congress on Hygiene, Berlin, 1907, Ravenel in a full discussion of the alimentary tract as a portal of entry for the tubercle bacillus concluded that the intestinal tract is a frequent portal of entrance for the tubercle bacillus, the bacilli being able to pass through an intact mucous membrane of the alimentary tract without giving rise to a local lesion. Such a mode of infection, he holds, is especially frequent in children, the source of infection being milk from tuberculous cows. In our present state of knowledge the exact proportion of cases of tuberculosis due to this cause cannot be stated, but it is probably considerable.

With Ravenel's conclusions the majority of pathologists and clinicians will probably agree. An unprejudiced survey of the recent literature compels us to accept the possibility of both modes of infection, inhalation and ingestion. Which is the more frequent or important we cannot say at the present time, and this important question urgently demands a settlement, since so many of the methods to be employed in the fight against tuberculosis hang upon the solution of this problem. Primary infection by way of the intestine has alone been considered in this article. It is only necessary here to call attention to the great importance of the intestinal tract as an avenue of re-infection in individuals whose sputum contains tubercle bacilli. Such patients should be warned against the dangers of swallowing sputum or saliva. Calmette's warning against the swallowing of saliva secreted during exposure to a dusty atmosphere is worthy of consideration as a measure tending to diminish the chances of infection, not only in the case of tuberculosis, but in that of other infections.

Alfred Scott Warthin.

TUMENOL-AMMONIUM is a derivative of tumenol, a product obtained from bituminous shale. It is a black semifluid substance with a spicy, tarry odor and acid taste, and is soluble in all proportions in water, alcohol, ether, and glycerin. It is especially recommended in eczema and itching dermatoses, and can be used as a tincture with alcohol, ether, and glycerin in the treatment of dry squamous eczema and erosions due to scratching; as a powder with zinc oxide and starch in acute forms of eczema; as an ointment with vaseline for severe itching dermatoses, and a paint with ether and tincture of benzoin for infiltrated or chronic eczema and furunculosis. Various solutions or mixtures are used, ranging from five to ten per cent. strength or more.

John W. Wainwright.

TUNBRIDGE WELLS.—Tunbridge Wells, a town of about 29,000 inhabitants, is pleasantly situated in the southern part of England, thirty-two miles southeast from London. It is a well-built town with broad streets and with a porous soil. The surrounding country is attractive and picturesque, affording many pleasant rides and walks.

The climate is comparatively dry and bracing and the air pure, so that an "after-cure" is not infrequently taken here. The mean temperature for the year is 49.8° F., the mean relative humidity 81 per cent., and the yearly rainfall 26.55 inches. The mean temperature for the four quarters of the year is as follows: January to March, 40.7°; April to June, 53.1°; July to September, 60.9°; October to December, 44.4°.

Considered as a climatic health resort, the air of this place has been found to be beneficial for conditions of lowered vitality and anemia, and in convalescence from severe illnesses. For the feeble, either in youth or old age, the climate is a favorable one, though it is rather cold in winter. It is said also to exercise a powerful restorative influence upon those wearied by city life and upon children brought up in large cities.

The waters are of the pure chalybeate class, containing 0.06 carbonate of iron per litre. There is no free carbonic-acid gas, the presence of which in the Continental chalybeate spas, such as Schwalbach, St. Moritz, etc., renders them available for bathing. Here the water is used only for drinking purposes. The water as it comes from the spring at a temperature of 51° F. is clear and not unpleasant to the taste.

But few visitors, however, come now to Tunbridge Wells to take the waters, although in old times it was a fashionable and much-frequented spa, when Bath was in its glory. It is rather upon its reputation as a health resort that its present popularity rests, for it is still crowded with visitors.

The chief mineral springs are situated at one end of the so-called "Pantiles," an old-fashioned paved promenade, on one side of which are shops and a covered way

for protection in rainy weather. The water is dispensed from two basins at a lower level than the pavement, and also in a reading room for visitors at the other end of the "Pantiles."

Anemia and debility are the two conditions treated by means of these waters. Sometimes in severe cases iron is prescribed in addition to that contained in the waters. The "cure" lasts two months and can be taken at any season of the year. The usual daily amount is a glass to a glass and a half, taken between eleven and one o'clock, in divided doses, with a short walk between. Of course in any condition in which iron is indicated these waters may be employed. No unpleasant effects are experienced from the use of the waters.

The chief season is from June to September. The accommodations are good and abundant. There are the usual out-door amusements, golf, cycling, rides, and drives.

Edward O. Otis.

TYPHOID FEVER, BACTERIOLOGY OF.—The bacillus of typhoid fever was discovered by Eberth in 1880, but not until four years later was it obtained in pure culture. This pure culture was isolated by Gaffky from the spleen and mesenteric lymph glands of patients dying from typhoid fever. In cover-slip preparations from pure cultures it stains well with any of the ordinary aniline dyes.

MORPHOLOGY.—The morphological characteristics of this organism are as follows: Its length varies from 1 to 4 μ , its diameter from 0.4 to 0.9 μ . The ends are always rounded. In cultures, and more especially in potato and old bouillon cultures, these organisms are often found grouped together in chains, sometimes as many as four or five in a chain. They are rapidly motile, this motility being due to the fact that they possess flagella, the number of which varies from eight to twenty. These flagella are attached to the bacillus at all points of its surface, that is, not only on the ends, as is the case in many bacteria, but also at its sides. For demonstrating these it is necessary to use a special method of staining. In my experience Loeffler's method has proved to be the best. Take two cover slips which have been thoroughly cleansed and are free from grease, and place on each one of these a drop of sterile water; then with a platinum needle touch the surface of an eighteen-hour agar culture of the bacillus, and draw the needle thus charged through first one drop and then the other; finally, cause the drop to spread out over a larger area and allow it to dry. By this method we obtain a good dilution in parts of the smears. There is no need to fix in the flame, as the mordant is a good fixative. The solutions required are as follows: First, a twenty-per-cent. aqueous solution of tannic acid; second, a saturated aqueous solution of ferrous sulphate (not to be heated); third, a saturated alcoholic solution of either fuchsin or gentian violet. Take of solution number one, ten parts; of number two, five parts; and of number three, one part. Let them stand for an hour and then filter; use at once. Flood the cover slip with this mordant (either of the first two solutions) for one minute, and then wash gently in distilled water; drain off the excess of water, and flood the slip with aniline fuchsin or aniline gentian violet, and warm carefully for one minute. Do not heat sufficiently to produce steam. Wash again in water and dry; then mount in Canada balsam. Another good method is that described by L. Smith in the *Journal of Medical Research*, vol. i., new series, p. 341. The dye which he uses is night blue; it gives a very beautiful picture, and is very easy to manage.

CULTURAL CHARACTERISTICS.—The bacillus grows best at body temperature (37.5° C.), but it grows well at room temperature. Its thermal death point is 60° C., after an exposure for twenty minutes. According to Park the organism will live for five months when frozen, but not longer. It grows well on all media. In bouillon it forms a uniform cloud throughout the tube, and often will develop a heavy pellicle on the surface. On agar it

produces a growth of a pearly white; on gelatin the growth is whitish and no liquefaction takes place; on potato the growth can hardly be seen at the end of forty-eight hours, but still older cultures may show a dirty-yellow growth. This organism grows well in milk without the production of acid from the lactose. There is, however, a slight primary production of acid. It does not coagulate the milk. In Dunham's solution it does not form indol. It does not cause any of the sugars to ferment with gas production. These last three cultural characteristics are used as a means of differentiating the typhoid bacillus from the colon and paracolon and the paratyphoid groups.

During the past few years there have been isolated from patients suffering from what seemed clinically to be a typhoid infection bacilli which did not answer culturally to the *Bacillus typhosus*, and did not agglutinate in serum which agglutinated this bacillus. The serum from the patient from which the organism had been isolated did not agglutinate the typhoid bacillus, but did agglutinate the isolated organism. These organisms when tested culturally behaved in some ways like the *B. typhosus*, while in other ways their behavior was like that of the *Bacillus coli communis*; hence they have been termed intermediates, and some bacteriologists have gone so far as to divide them into sub-groups. The organisms are often spoken of indiscriminately as para-typhoid or paracolon bacilli.

So many of these intermediates have been isolated that it will be impossible to discuss them all here. It might be stated, however, that the great majority of the cases suffering from infection with these intermediate organisms have run a very mild course, and they do not seem to be as pathogenic a group, on the whole, as that of the *Bacillus typhosus*.

The following short table will give a good idea of the position of this group:

	Bacillus typhosus.	Inter-mediates.	Colon bacillus.
1. Formation of indol in Dunham's solution in forty-eight hours.	Negative results.	Some positive results.	Positive results.
2. Coagulation of milk	Negative results.	Negative results.	Positive results.
3. Fermentation with production of gas in—			
(a) glucose bouillon	Negative results.	Positive results.	Positive results.
(b) lactose bouillon	Negative results.	No positive results.	Positive results.
(c) mannit bouillon.	Negative results.	Some positive results.	Positive results.
4. Agglutination with specific serum—			
(a) typhoid serum	Positive results.	Negative results.	Negative results.
(b) intermediate serum	Negative results.	Positive results.	Negative results.
(c) colon serum.	Negative results.	Negative result.	Positive results.

Of the intermediates which have thus far been isolated, the following are among the more important, historically as well as bacteriologically: Gaertner's, Cushing's, Gwyn's, Schottmüller's, Buxton's, and Libman's.

AGGLUTINATION.—This phenomenon does not belong exclusively to the subject of this article, but I shall treat of it fully for two reasons: first, because it was the study of this reaction with the *B. typhosus* that stimulated a great amount of research in regard to this phenomenon as an aid to diagnosis; secondly, because of the importance of this test and on account of the many errors to which it may lead unless it be fully understood. In 1884 Charrin and Roger, while working with the *Bacillus pyocyaneus*, observed the clumping of the bacilli, but they pushed their study of this phenomenon no further, and it was not till 1896 that it was again brought forward, this time by Gruber and Durham. These investigators immunized animals against various strains of

bacteria, and they found that the serum of these animals had the property of clumping the bacteria when the bacteria were brought in contact with it; and, furthermore, they found that this action was fairly specific, that is, the serum from any animal which they had immunized would only clump the species of bacteria which had been used to bring about this immunization. They therefore advocated that this phenomenon be utilized for the purpose of differentiating species of bacteria. They did not, however, in their published work, suggest the use of serum taken from these patients as a means of determining what species of bacteria were causing the infection.

During this same year (1896) there was published a paper by Widal and Grünbaum in which they outlined a clinical test for typhoid fever based on the phenomenon of clumping. They were the first, therefore, to point out the value as a means of diagnosis, and the first also to devise a technique for carrying out the test. Since their paper was published this test has been used in all parts of the world, and legion are the papers that have been published on it.

THE TECHNIQUE.—The requisites are: 1. An actively motile culture of *B. typhosus*. This is best obtained by emulsifying a twenty-four hours' old agar culture in 10 c.c. of an 0.85 per cent. sodium-chloride solution; or by transferring from three to six loopfuls of a twenty-four-hour agar culture to a tube containing bouillon, shaking this thoroughly and incubating at 37° C. for an hour or two; or else one may transplant the typhoid bacilli from day to day into tubes of bouillon and let the growth proceed on the top of the thermostat. 2. The blood to be tested may either be in a dried condition or else it may be collected in capillary tubes and the serum obtained from these after coagulation. By the latter method we can measure our dilutions with almost perfect accuracy, a thing which it is impossible to do if we use a dried specimen. In the latter case it is necessary to dissolve out the substance representing the serum by letting the water used for the solvent completely surround the dried spot or stain. Then be careful not to move hastily or rub any of the clot loose. Only in this way is it possible to obtain a serum free from fibrin and blood corpuscles.

The mixture of the culture and serum may be observed in two ways: First, in the test tube; and, second, in the hanging drop. For the latter test are needed a microscope with a No. 3 or a No. 4 eyepiece, a one-sixth or one-seventh objective, hollow-ground slides, and absolutely clean cover slips (No. 1 or No. 2). Surround the hollow on the slide with vaseline or alboline, so that when the cover slip is placed over it its edges will be sealed, and thus evaporation will be prevented.

In the hanging-drop method, one drop of the fluid containing the bacteria, and one drop of the serum fluid are mixed on the cover slip and examined. In my experience the hanging-drop method is the most accurate if it be properly controlled. In the test tube the reaction is apparent to the naked eye, for when the organisms are clumped they collect at the bottom of the tube in a flocculent mass.

The clumping of the bacilli should take place in thirty minutes with a dilution of 1 to 20; if it takes more than thirty minutes or a dilution of less than 1 to 20, it should not be regarded in the light of a positive reaction, for it may then be due to a number of other factors which are too numerous to mention here. Some specimens of serum will not agglutinate in a dilution of 1 to 20, but will do so if the dilution be increased 1 to 50.

Instead of a clumping of the bacilli we may have what is known as a thread reaction; that is, the bacilli become arranged end to end, or, failing to separate completely as they multiply, they remain in the form of threads or chains.

THE DISTRIBUTION OF THE TYPHOID BACILLI IN THE BODY.—These organisms are found in the different tissues and fluids of the body as well as in the contents of the intestinal canal. We will consider these different localities in regular order, but in a very brief manner.

The Blood.—The typhoid bacilli are found with the greatest constancy in the blood. In the earlier examinations the search for these organisms in the blood gave very unsatisfactory results. At a later date, however, it was found that by the use of blood in bouillon highly diluted the presence of the bacilli could be demonstrated in the great majority of cases.

The Spleen.—Masses of the bacteria are found in the sinuses of the spleen, and splenic puncture has been recommended as a means of securing an early diagnosis. Such an exploratory puncture, however, is not free from danger to the patient, and the procedure is therefore not to be recommended.

The Rose Spots.—The bacilli may be obtained from these spots as early as on the seventh or eighth day apparently, in most instances, before the development, in the blood, of the substances which give rise to the Widal reaction (Hiss).

The Intestines and Their Contents.—It is here that the bacilli make their earliest appearance in the majority of cases. They are constantly found in Peyer's patches, and more particularly at the base of those which are ulcerated. They pass from these tissues doubtless by way of the lymphatics, and find lodgment in the mesenteric lymph nodes. Many of them are found in the phagocytic cells of the lymphatic system and also in the fixed phagocytic connective-tissue cells of the spleen. They are found also in large numbers in the faeces.

The Liver.—In this organ there have been observed small areas of degeneration, which have been termed focal necroses. They are caused by the lodgment of the bacilli at these points, and as these organisms grow their toxin causes a degeneration of the cells surrounding them. According to some reports the bacilli have been found in the gall bladder many years after an attack of typhoid fever, and it is even believed by some writers that they furnish a nucleus for the formation of gall stones. Bile often causes an agglutination of the bacilli.

The Kidneys and the Urine.—The bacilli have been demonstrated in the kidneys, and they are found in the urine in about twenty-five per cent. of the cases, but not before the fourteenth or fifteenth day of the disease; in fact, they are not to be found in the urine in some cases until convalescence is established. According to most observers the bacilli may persist in the urine for days or even weeks. It is even claimed by some authorities that they continue to be present in the urine for a period of several months.

The Mouth and Throat.—The finding of typhoid bacilli by Besson in the tonsils of six out of ten patients investigated warrants the belief that they also exist in the mouth.

The Lungs.—In some rare cases in which there has been a pneumonic form of infection, the bacilli have been found in the lungs. Indeed, in those cases in which an overwhelming blood infection—in other words, a septicæmia—occurs, they will be found in all the tissues of the body.

As the infection is not symmetrically distributed in all cases, there can be no one method of securing an early diagnosis. Hence, if he wishes to make a sure bacteriological diagnosis, the bacteriologist must take time, and it often happens that the clinician can be fairly certain of his diagnosis before he hears from the laboratory. Nevertheless, a bacteriological diagnosis is most important as a means of corroborating the clinical diagnosis.

Animals infected with *B. typhosus* have developed only in rare instances a disease at all comparable to that in man. So far as practical serum therapy is concerned, it has ever, in this disease, shown negative results.

MEDIA USED AS AN AID TO THE ISOLATION OF THE BACILLUS TYPHOSUS.—Many different media have been devised for use in isolating this organism, but there are only four which have stood the test of time, and which, in the hands of the trained bacteriologist, are admitted to be more or less effective in isolating the typhoid bacilli. The simplest one is that devised by Hiss. For complet-

ing the differentiation, however, Hiss uses two different media. His first step is to plate out some of the suspected material in a medium the composition of which is as follows:

Hiss' Plating Medium.

	Gm.
Agar	15.
Gelatin	15.
Liebig's extract	5.
Sodium chloride.....	5.
Dextrose	10.
Distilled water	1,000.

The agar is first melted and then the rest of the ingredients are added. After the mixture has boiled for a few minutes, it is allowed to cool and is cleared with the white of two eggs. Then it should be boiled again and filtered through a thin layer of absorbent cotton. Before filtering see that the total amount of fluid is 1,000 c.c.; and, if it be found to be less than this amount, add enough hot distilled water to bring it up to that point.

I have found that this is one of the most important points in making up this plating medium. No acid or alkali need be added to the mixture.

In this plating medium the typhoid colonies form thready growths, while the colon colonies are round with smooth edges. The colonies showing threads are fished out and plated in Hiss' tube medium, which is composed as follows:

Hiss' Tube Medium.

	Gm.
Agar	5.
Gelatin	80.
Liebig's extract	5.
Sodium chloride.....	5.
Dextrose	10.
Distilled water.....	1,000.

This medium differs from the first, as will be observed, in having 10 gm. less of agar and 65 gm. more of gelatin. The mixture is also cleared with the white of two eggs and is corrected to 1.5 acid, phenolphthalein being the indicator.

In this tube medium the *Bacillus typhosus* clouds it throughout in twenty-four hours. *B. coli* generally shows growth and gas formation only along the line of puncture. This medium has given us many excellent results, and I prefer it to all the others.

Elsner's Method (after Park).—1st. Grate 0.5 kgm. of small potatoes to a fine pulp and add one litre of cold water; let it stand over night in a cool place.

2d. Wash thoroughly and strain through a fine cloth. This must be done while the mixture is cold.

3d. Boil the filtrates and filter again.

4th. Add ten per cent. of gelatin and boil until it is dissolved.

5th. Test the acidity and have it so that 3 c.c. of a decinormal sodium-hydrate solution will neutralize 10 c.c. of the medium, phenolphthalein being the indicator.

6th. Boil and clear with egg.

7th. Filter through cotton and then through paper.

8th. To the filtrate add one per cent. of potassium iodide. (Use a solution so made that 1 c.c. shall contain 1 gm. of the salt.)

9th. Decant into tubes and sterilize.

The incubator for this medium must be kept at from 22° to 24° C.

The plates must be thoroughly cooled before placing in the incubator, as otherwise the difference between *B. typhosus* and *B. coli* would not be observed.

The colon colonies are the first to develop. They are rough and granular, and have a greenish-brown color; later, the typhoid colonies develop and are small, white, and gleaming, and can best be described as being dew-drop-like in appearance, although occasionally somewhat granular. This is apt to cause some confusion in the mind of the beginner, but one who is familiar with the

use of this medium is very little likely to make a mistake. The potassium iodide prevents nearly all other organisms from developing in this medium.

This plating medium, used in conjunction with Hiss' tube medium, gives us a very satisfactory differential method.

The Capaldi plating medium and that formulated by von Drigalski and Conradi have in my hands furnished such variable results that I scarcely think it necessary to describe them here. The latter is a very complicated medium, by no means easy to prepare.

Distribution of the Bacilli Outside the Body.—The *Bacillus typhosus* may remain in contaminated soil for from two to three months, and in water for nearly the same length of time. On the other hand, if either the soil or the water contains enough organic matter for the support of the organism, it may remain there indefinitely.

The past few years have witnessed no change in our ideas regarding the transmission of typhoid fever. In fact, the theories of that time have merely been strengthened, and all are now agreed that in the vast majority of cases it is through the alimentary tract that the infection gains entrance to our system. In a few rare instances it is believed that the infection has been brought about by the inhalation of the *Bacillus typhosus* into the lungs.

There still remain to be considered the different methods by which this organism can gain entrance to the intestines. First, we may have a direct infection, that is, from a person suffering from the disease to one who has come in contact with the patient. When infection occurs in this manner some infected material must pass, through carelessness, to the alimentary canal of the individual contracting the disease; for, if perfect cleanliness and caution are observed, this form of infection need never occur.

Unless the excreta of the patient be thoroughly disinfected they will pollute the soil, and the infective organisms which they contain will remain quiescent until they are washed into some water supply, from which they gain entrance into some other human being. This may happen in any of the following ways: directly, as in drinking water or in ice, or in milk to which contaminated water has been added, either for purposes of dilution or in cleansing the receptacle. In milk the bacilli will multiply rapidly, unless the milk be kept constantly iced. If there be a large source of pollution, from which the polluted material drains into a river or creek, the submerged banks of which are used for the fattening of oysters, these will take in the bacilli and will furnish them, if decomposition should begin to develop in the host, with a soil most favorable for their rapid multiplication. It is under these circumstances that oysters may serve as the source of typhoid infection among those who eat them in an uncooked state. (At some later date the author proposes to publish the experiments which he has made in this special field.)

If the excreta be thrown into sinks and privies where flies congregate in large numbers, these insects will transfer the infected material to the house—i.e., they will deposit it upon any food, cooked or uncooked, to which they may gain access. This is probably a frequent mode of spreading typhoid infection among the different members of a family after one of their number has been taken ill with the disease. Nothing short of the most thorough disinfection will prevent such a spreading of typhoid fever.

Raw vegetables may serve as carriers of the disease provided they have been watered with infected material or have been washed in infected water, in preparation for their appearance on the table.

Ice cream, when manufactured of milk or cream which contains typhoid bacilli, and which has not been cooked, may serve to communicate the disease.

Major Firth, of the English Army Medical Corps, has recently shown that clothing which has been soiled by the excreta of a patient suffering with this disease may retain the virulent typhoid bacilli at the end of eighty-

four days. Consequently soiled clothing, unless disinfected, may be a means of spreading the disease. The same authority has also shown that the bacilli may remain fully virulent in the soil for eighty-five days, and we know from other observations that it can remain so for much longer periods. Major Firth also claims that they may retain their virulence for twenty-five days after having been dried and blown about as dust. If this be so, it is certainly a matter of great importance, for it shows that the typhoid bacillus is a much more resistant organism than we have given it credit for being. This observation, however, must first be confirmed by other authorities before we can accept it as a fact.

To sum up, then, we find that there are three great roads by which infection reaches human beings. These are, first, personal contamination from person to person; second, contamination of water supply and therefore of milk and food; and third, the spread of the bacilli by household insects such as flies, cockroaches, etc. [See also the article on *Bacilli Carriers* in the REFERENCE HANDBOOK, vol. viii., page 405.]

From this it will be seen that the great weapons for combating the spread of this disease are, first, thorough disinfection of all excreta from the patient (including the urine); second, the thorough sanitary supervision of our water supplies so that our water-sheds may escape contamination.

Cyrus West Field.

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URINARY SEGREGATION.—Present-day renal surgery demands that no kidney be made the subject of operative intervention unless its condition is known, and the functionability of its fellow established. The rapid advance in diagnostic methods has, in the past twenty years, produced a number of procedures to obtain the urine separately from each kidney. The separate urines secured can be examined separately for evidence of the condition of each kidney. The other methods of diagnosing renal disease may be considered as complementary to separate urinalysis, though in many if not all cases they are of transcendent importance. The principal methods are: 1, radiography; 2, intravesical separation or segregation of the urines; 3, ureteral catheterism; 4, microscopic and chemical urinalysis; 5, the phloridzin test; 6, cryoscopy. The less precise but often useful method, palpation of the kidneys and ureters, has not been crowded into disuse by the newer and more exact ones. For the sake of as much completeness as is possible it is here noted that the ureters can often be palpated through the vagina and the rectum. An almost separate place is occupied by ureteric meatoscopy.

The principal reasons for one or more of these examinations are: the surgical treatment of acute or chronic nephritis; the removal of renal or ureteral calculi; nephropexy; removal of the kidney when destroyed by suppuration beyond usefulness; renal tuberculosis; malignant disease; differentiation of those vesical diseases that may simulate renal affections, as epithelioma encroaching upon the mouth of a ureter, infection ascending the ureter from the bladder, a benign growth (papilloma) or simple ulcer near the ureteral meatus; calculus wedged into the ureter; vesical and penile manifestations of renal disease, otherwise symptomless hæmaturia, pyuria, and chyluria; diseases of neighbor-

ing organs that may simulate vesical, ureteral, and renal affections, as appendicitis, diseases or displacements of the female genitalia.

Radiography (*vide* Vol. VI., p. 989, *Calculi*).—When for any reason, such as stricture of the ureter, a laterally very much enlarged prostate, a vesical neoplasm, copious, imminently dangerous hæmaturia, etc., the urine separately from each kidney cannot be obtained, expert radiography can quickly indicate which kidney is diseased and, in many instances, even the character of disease or deformity, *e.g.*, stone, cancer, single kidney, horseshoe kidney, etc. Radiography is also valuable as a confirmatory means of diagnosis, even when separation of the urines is perfectly performed. It is especially valuable in combination with ureteral catheterism when ureteral kinking or sigmate ureter (Gallant) does not materially impede ureteral catheterism and the distortion consequently is not evident. Radiography, then, with a metal ureteral sound, or a stylette in the ureteral catheter, will serve to reveal the ureter's abnormal course.

Beck,¹ in describing his technique of localizing renal and ureteral calculi, says: "It is one of the strange phenomena in medicine that, in the face of the most abundant proofs of the reliability of renal skiagraphy, some of the best text-books still hesitate to recommend the method; some others even openly warn the practitioner against it. . . . Whatever errors have been committed were of the individual, not of the method. . . . A definite diagnosis in suspected lithiasis can be made in each and every instance."

Means and methods of diagnosis not predicated upon obtaining the urines separately from each kidney are discussed under their respective heads in various parts of this work. Reference to them will be made whenever necessary to complement the special subject.

Ureteric meatoscopy, although not dependent upon obtaining the separate urines, merits consideration together with the subject in hand. Inspection of the ureteral meatus, whether altered in shape, thickness, color; its action in ejecting urine, clear or with perceptible abnormal mixtures, was developed into a science by Fenwick² as a result of a vast number of cystoscopies. This aid to diagnosis is, however, necessarily reserved to those few gifted with extraordinary powers of observation and special ability for visual differentiation, in addition to remarkable skill in correcting that distortion of the image which inevitably results from even the slightest misdirection of the cystoscopic lens. The value of Fenwick's meatoscopy to those who cannot attain his skill is essentially in the guide it gives to avoiding ureteral catheterism of the healthy side and consequently safeguarding it from the risks of inevitable slight traumatism and possible infection. That Fenwick's method is not illusory is proven by his large list of published cases, in which the diagnosis made by ureteric meatoscopy was confirmed by subsequent operation.

Segregators are ingenious developments from the now naturally discarded methods of manual or mechanical compression by means of which it formerly was attempted to occlude one ureter for the purpose of obtaining unmixed the urine from the other.

The principal types of segregators are the Harris instrument and the Downes separate-urine siphon. Harris³ described the principle underlying his device as follows: "The segregator takes advantage of the anatomic fact of the separateness of the ureters as they enter the bladder, and by mechanically prolonging them to the exterior of the body segregates the urines into separate vials."

The employment of the *Harris segregator* may be briefly described by condensing the author's directions for its use.⁴ "The patient . . . is placed comfortably on a table in the ordinary lithotomy position, with the hips slightly elevated. The instrument, with the flattened surfaces in contact so as to form practically a single catheter (Fig. 3078, Vol. V., p. 355), is introduced

into the bladder in the ordinary way. So soon as the proximal, curved extremity is within the bladder . . . each catheter (contained in the external sheath) is rotated about its longitudinal axis until its proximal end, as indicated by its distal end, is directed outward and backward (Fig. 3079, Vol. V., p. 356). . . . They are then held in position by a small spiral spring. . . . The lever (Fig. 3080, Vol. V., p. 356) is now introduced into the vagina in the female or rectum in the male. By gentle pressure forward directly in the mid-line, the base of the bladder is raised into a longitudinal fold between the ureteral openings. . . . The end of each catheter now lies at the most dependent part of a little pocket, a perfect watershed separating the two. . . . By producing a gentle exhaustion of the air in the vials by means of the bulb, the urine, as fast as it escapes from the ureters, . . . flows at once into the vials, right and left respectively."

The *Downes separate-urine siphon* was presented⁵ as "an improvement on the Harris instrument, simpler in construction, requiring no suction apparatus and relying upon siphonage alone for obtaining the urines separately from each kidney." Recent forms of this instrument (Fig. 5276) obviate the necessity of rotating the beaks, which turn after insertion, 21½ degrees from the central base-line of the bladder. The enlarged intravesical end of each beak has a number of perforations, which



FIG. 5276.—Downes' Separate-Urine Siphon.

transmit the urine into the sulci formed at each side of the mesial line by the lever (see Fig. 5276) in the vagina or rectum. The sulci or watersheds so formed give their contents to an "egress-opening" traversing each catheter, through which they are siphoned to receptacles prepared to receive them. The author presents numerous tests of the efficacy of his separate-urine siphon; these tests are identical with those presented by the other instruments devised for the same purpose. He concedes, however, that it "is not as useful in the male bladder."

Cathelin's divisor and *Luys' separator* are modern developments from several instruments, most of which were purely experimental.

Cathelin's graduated vesical divisor (to condense from a paper by the present writer⁶) relies essentially upon a delicate rubber membrane, set into a very fine steel frame, which, when pushed into the bladder, adapts itself to all the inequalities of its inner surface, and vertically partitions the viscus into two equal halves (Fig. 5277). Catheters projecting into each half carry the urine from each ureter through the instrument to separate vials that receive it separately. The mechanism by which this is accomplished consists of a narrow shaft terminating as a short-beaked catheter. The upper surface of the shaft is partly grooved to slightly beyond its curved beak; thenceforward to its distal extremity it is a closed canal. The closed canal allows free transmission of the stem to which the spring with its rubber membrane is attached. Withdrawal of the stem folds the membrane into the shaft; pushing it forward thrusts the spring with its membrane into the bladder, allows it to unfold itself vertically and to fit itself to the bladder walls. The shaft of the newest model grasps two metal catheters, which are turned from the central shaft to siphon the urine separately as it escapes from the ureters (Fig. 5278).

Discussing the means of obtaining the separate urines from each kidney, Cathelin⁷ emphasizes that the af-

infected kidney in renal tuberculosis is rarely large or distended; consequently palpation cannot, in such case, reveal which kidney is involved. Furthermore, pain, which is not always present, is a deceptive guide, as

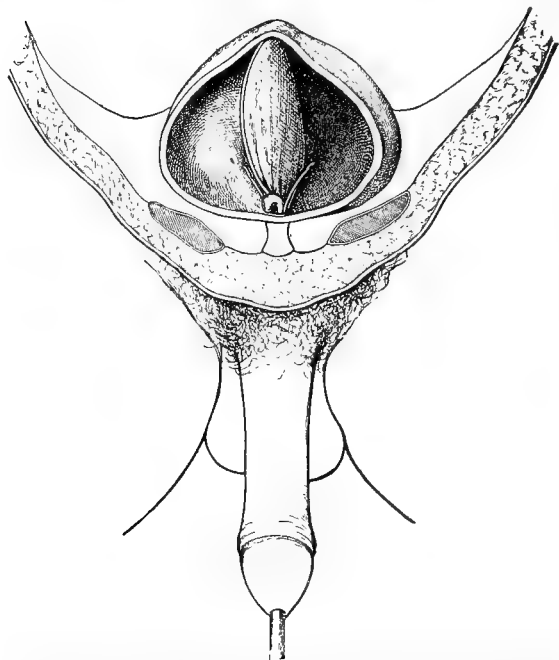


FIG. 5277.—The Membrane of Cathelin's Instrument Dividing the Bladder into two Compartments; each of the catheters in its respective chamber.

when present it may be referred to the opposite side. The uncertainty remains even after cystoscopy and ureteric meatoscopy. So also pain on ureteral pressure at the umbilical or iliac levels, or that produced by ureteral palpation through the rectum or vagina, may fail to determine which kidney is affected.

Cathelin further insists that inasmuch as in nearly all cases of even beginning renal tuberculosis the bladder is infected, ureteral catheterism endangers the healthy

valve and by the erosions the catheter may produce along the pyelo-ureteral mucosa. That such traumatism or erosion or both occur is evident from the slight

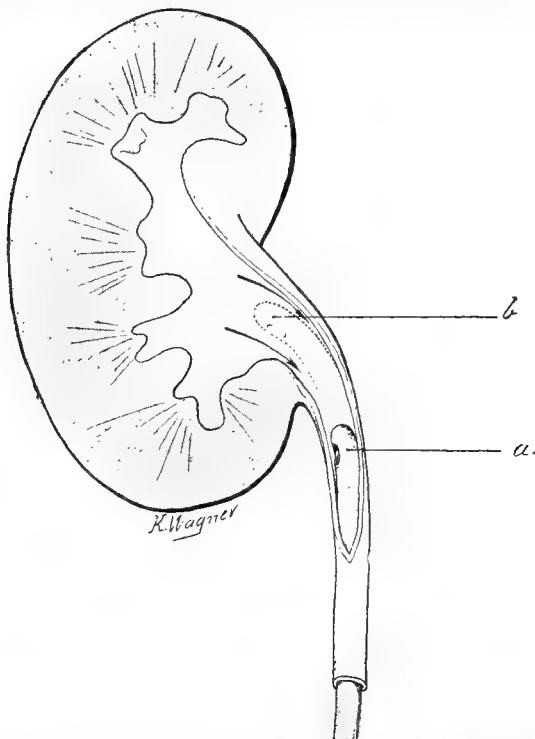


FIG. 5279.—Schematic Design to Show Possibility of a Part of the Urine Escaping from Renal Pelvis alongside the ureteral catheter at *a* and *b* while another part of the urine is drained off by the catheter.

bleeding which is nearly always provoked by ureteral catheterism even when performed with the greatest possible gentleness and in a healthy subject.

Cathelin also insists that the ureteral catheter does not always sufficiently block the ureter to prevent seeping of urine between it and the ureter. He shows this in a schematic drawing (Fig. 5279). To the writer this objection does not seem as cogent as do the others which Cathelin advances. The percolation of urine alongside the ureteral catheter is avoidable by using an instrument of proper calibre when the rhythmical contractions of the ureter do not suffice firmly to grasp the catheter. In cases, as of ureteral stricture, where a sufficiently large catheter cannot be passed, or where ureteral peristalsis is abolished, Nitze's ballooning ureteral catheter will certainly arrest the flow of urine in any other course except through the catheter.

In another schematic drawing (Fig. 5280) Cathelin presents an additional argument against ureteral catheterism. He distinctly reproaches the ureteral catheter with inability to drain completely a renal retention, which he deems a likely cause of error in diagnosis and

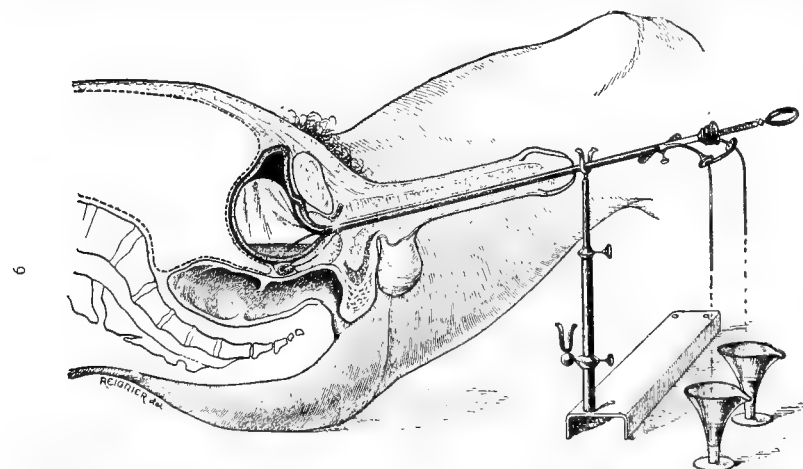


FIG. 5278.—Cathelin's Intravesical Divisor *in situ*. The light intravesical part is the soft-rubber septum, dividing the bladder into two chambers; the catheter is shown projecting into the right chamber, close to the ureteral opening, automatically siphoning the urine therefrom.

kidney; not necessarily by the carrying of microbes along with the catheter from the infected bladder, but by the traumatism inflicted on traversing the ureteral

treatment. It seems to the present writer that Cathelin does not here consider the great pliability of the ureteral catheter, which pliability is vastly increased by

the body heat as the instrument traverses the ureter. This may cause the catheter to bend along the inner walls of the renal pelvis, without materially injuring it, and, if propelled sufficiently, to dip its eye as deep as

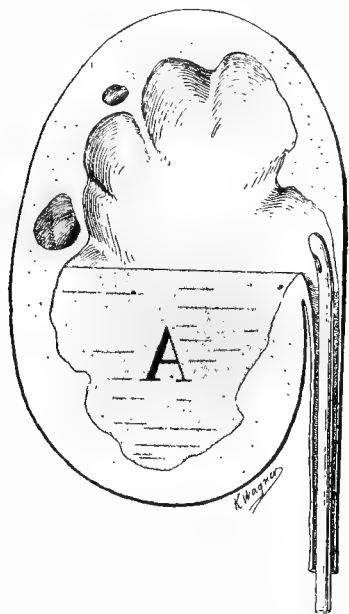


FIG. 5280.—Diagram to Show how a Ureteral Catheter may not Drain a Pouch of Renal Retention.

necessary into the expanded ureteral pelvis (see Fig. 5280, A) to drain it of the urine retained. Even should this not suffice to accomplish the end in view, raising the enlarged kidney will dip the catheter's tip into the retained urine. In practice the prompt results of ureteral catheterism in renal retention are too well known to merit discussion.

Cathelin, however, does not discard ureteral catheterism or any of the other methods of differentiation between the healthy and the diseased kidney; for, while he gives preference to his divisor, he broadly holds that each procedure has its place in suitable cases.

Luys⁸ describes his separator as consisting of a central metallic staff, with a beak curved like that of the Guyon sound (Fig. 5281). In the beak's concavity and fastened to its tip is a chain similar to a chain-saw, which is rendered taut or slack by means of the screw-head at the distal extremity. This central staff is inserted into a soft-rubber cover. Two metallic catheters flattened on their inner surfaces, and curved like the central staff, with three orifices in each for the escape of urine, are attached to the central staff, into the handle, and by a smooth screw-cap at the tip (Fig. 5282). The instrument so assembled has a calibre of 22 F. A



FIG. 5281.—The Luys Separator, Mounted: Showing the Membrane in Place and Detached.

smaller separator (15 F.) with a more markedly curved beak is used for children. Luys recites one instance of a girl six and one-half years old, and another of nine in whom he successfully obtained the separate urines by means of this instrument. In both cases he was thus

enabled to diagnose left pyonephrosis. In these cases the separator was left in place for fifteen and twenty minutes respectively.

Luys advises the injection of several cubic centimetres of one-per-cent. stovain into the deep urethra several minutes before inserting the instrument, when the membranous portion is exceedingly sensitive, or when dealing with a pusillanimous subject. In some cases he deems it well to administer a small rectal injection containing a gram of antipyrin with several drops of laudanum about an hour before using the instrument. He further advises that the bowels be emptied, lest intestinal peristalsis produce such pain as to compel interruption of the separation. Except in cases of renal hematuria, the author advises a subcutaneous injection of a cubic centimetre of five per cent. of methylene blue in sterilized water, two hours before the separation, to determine renal permeability.

The instrument is inserted in the manner usually employed for the Guyon sounds. Two fingers stop the catheters that project at the handle, while the screw-head is turned to its fullest extent, rendering the chain tense and thus raising the rubber cover into a fold which divides the lower part of the bladder. To prevent mixing the urines from each kidney, the curved end of the separator is pressed to the base of the bladder. The back of the operating table is then elevated to raise the patient into the sitting position; his or her legs are then placed into stirrups at either side of the table's foot-board, and the handle of the separator rested upon a support, which also has vials to receive the urine as it drips from each catheter (Fig. 5283). Luys, however, does not regularly use this support, as the hand can better keep the curve of the separator in close contact with the vesical neck. The author says (*op. cit.*, p. 425) that he has often left his separator in place for forty-five

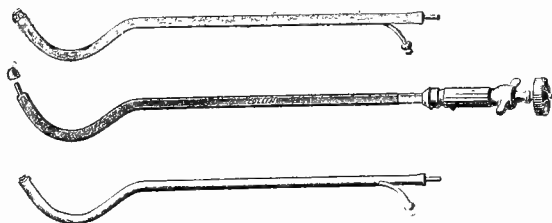


FIG. 5282.—The Luys Separator, Dismounted; Showing the Various Parts.

minutes to an hour, without in the slightest degree inconveniencing the patient.

Luys claims the following advantages for intravesical separation of the urine over ureteral catheterism: 1, that it is simpler; 2, that it can be employed in a greater number of cases; 3, that it entails no dangers; and 4, that the information derived when the instrument is properly employed is, if not better, at least as rigorously precise as that furnished by ureteral catheterism.

Vale⁹ of Washington advances the following points of superiority for the Luys separator: "Its simplicity and freedom from all danger reduces urinary separation from the dignity of an operation to a procedure. . . . Tuberculosis of one kidney or an infected bladder do not constitute contraindications to urinary separation with this instrument. In children, in prostatitis, and in patients with a reduced bladder capacity it is successful, when catheterization may be impossible. Among Luys' cases, however, I find one in which separation could not be effected, because the use of any instrument caused bleeding in passing the prostate, and the blood-clots plugged the mouths of the catheters."

v. Frisch¹⁰ thus sums up consideration of the instruments mentioned. "None of these apparatus positively insures against mixture of urine from both sides. . . . The slightest change of shape of the prostate produces quite unreliable results. Moreover, none of these in-

struments is applicable in severe, especially ulcerative, affections of the bladder, in which we must count on admixture of catarrhal secretions and blood, even though the bladder has been previously irrigated as thoroughly as possible. The problem to separate the urine from each kidney in an unexceptionable manner could be solved only by direct ureteral catheterism." Despite this authoritative condemnation of divisors, separators, segregators etc., it is undeniable that, in the hands of the authors and those directly instructed



FIG. 5283.—The Luys Separator in Operation. The sitting position is necessary in order to have the separation complete.

by them, the urine from each kidney is successfully obtained.

Still, those who are not deterred by the apparently complicated character of the ureter-catheterizing cystoscope, and who are conscious of possessing a certain amount of manual dexterity, prefer

Ureteral catheterism to other means of obtaining separate urines from each kidney.

Aside from all other considerations, ureteral catheterism possesses an advantage not available to the other methods. The others, even when acting perfectly and in an extremely tolerant bladder, cannot be employed, at the utmost, beyond thirty minutes. This is denied by Luys, who separated the urine for a whole hour. Even then the urines so obtained represent only the amount secreted during that time. Ureteral catheters can be retained for twenty-four or even forty-eight hours, and can then be removed and replaced by others with only the loss of that little urine which escapes between the removal of one catheter and the insertion of another. Thus the entire quantity of urine for twenty-four hours from each kidney can be obtained for examination, and the act repeated as often as may be necessary for an absolute diagnosis and the treatment of unilateral ureteral or renal conditions, when they do not require major surgical intervention.

As readily performed and as well borne as ureteral catheterism is in the majority of cases, it is by no means

always an innocuous procedure. Nitze, in his posthumous work,¹¹ emphasizes that it "is not a harmless intervention, but a more or less dangerous one." He concludes that the danger is minimal when the urethra, bladder, and kidneys are normal, but adds that then the intervention is unnecessary. Manifestly, when a cystoscope carrying a ureteral catheter traverses an infected urethra or bladder it is only a matter of accident when the ureter is not infected thereby. On the other hand, it is undeniable that in the very cases in which ureteral catheterism is most valuable for diagnostic purposes its dangers are considerable. Nitze points out that it is permissible only when the operator is positive that the intervention will result in a certitude which is a gain for the patient greater than the danger to which ureteral catheterism exposes him.

Before Nitze's genius gave the profession his perfected catheterizing cystoscope, a number of methods and instruments had been devised to the same end; their interest is now but historic. Since Nitze's first presentation of his catheterizing cystoscope, a number of other instruments for the same purposes have been offered the profession.

The Kelly tube, without the aid of an optical apparatus, and by postural air-dilatation of the bladder, exposes the ureteral mouths to reflected light. The latter is not a *sine qua non*, as the present writer witnessed Kelly catheterize both ureters by means of the Valentine urethroscope in March, 1899. The instruments used by Kelly, and the technique of ureteral catheterism as practised by him, are fully described in Vol. I., p. 778 *et seq.*, of this work. The question of priority in visual ureteral catheterism through the urethra is briefly disposed of by Fuller:¹² "Although Kelly was not the originator of the method he employs, Pawlick and Neumann being his predecessors, still he has done so much in the way of developing ideas and making the procedure practical that it is proper to give him chief credit."

Kelly, by lengthening his tube, endeavored to extend its usefulness to catheterism of the male ureters. Attempts made by others to use this instrument in any but female patients have not proven successful.

Luys⁸ presents as his cystoscope a lengthened Valentine urethroscope, which was discarded by the present writer when in practice its inefficiency for bladder work became evident.

Many other instruments for dilating the bladder with air for cystoscopy and ureteral catheterism have been devised. Some of these are arranged for use with air or water; some are essentially tubes carrying a Nitze intravesical light; others have as an optical apparatus an adaptation of the terrestrial telescope, arranged to augment the field of vision. All, however, serve to demonstrate the uncertainty of air as a vesical dilating medium, except when used with the Kelly tube in females.

The essential difference between the two general forms of ureter-catheterizing cystoscopes is in the manner in which the ureteral catheter is directed after its tip has been projected out of the canal carrying it.

The Nitze cystoscopy accomplishes this by means of the Albarrán "onglet," a little lever shaped somewhat like a human finger-nail, by which any desired angle can be given to the ureteral catheter by means of a screw near the ocular end of the cystoscope (Fig. 5284).

Nitze's cystoscope for simultaneous catheterism of both ureters is provided with double catheter-carriers (Fig. 5285), which improvement Nitze attributes to Lohnstein. In performing bilateral ureteral catheterism the present writer prefers to use catheters of distinctly different colors, to render intravesical manipulation thereof easier. F. Tilden Brown has further essentially modified Lohnstein's modification by adding an irrigating attachment to the double-catheterizing instrument. It is illustrated in Fig. 3068, Vol. V., p. 349.

Albarrán's cystoscope, from which the onglet used in most modern ureteral catheterizing instruments is de-

rived, differs from the Nitze instrument in that his (Albarrán's) simple exploring cystoscope can be converted into either a catheterizing or irrigating instrument by merely clasp[ing] thereon separate attachments for each purpose.

Casper's ureter cystoscope¹³ differs from those mentioned in that the varying curves of the catheter are pro-

intweit, Freudenberg, and numerous others. Each has special advantages in minor additions; the principle underlying every one is according to the original design of either Nitze, Casper, or Albarrán, and differs accordingly from the others.

The selection of an instrument for ureteral catheterism is essentially a matter of personal preference. The

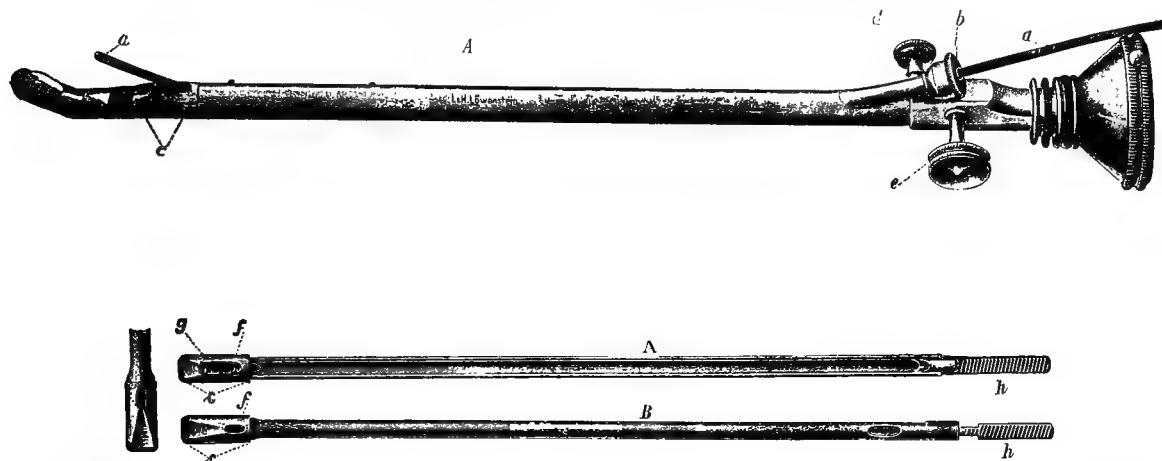


FIG. 5284.—Nitze Ureter-Catheterizing Cystoscope, Convertible into an Irrigating Cystoscope by Removing the Staff A (which carries the Ureteral Catheter) and Attaching the Staff B in its Place. Staff A shows the movable "onglet" (c); by moving the screw e it acts as a lever, curving the ureteral catheter a to the angle necessary to permit its insertion into the ureter. After the tip of the catheter is engaged in the ureteral mouth the screw e is turned to flatten down the onglet to its place, freeing the catheter from all friction and enabling its easy projection into the ureter as far as needed.

duced by a tubular slide moving the entire length of a gutter that occupies the upper surface of the cystoscope. The further the slide is thrust forward the more closely does it press the protruding catheter toward the head of the cystoscope; in thus pressing it bends the catheter to an angle the more acute the tighter the pressure ex-

writer has witnessed nearly every one of the authors use his instrument, and in each instance with commendable celerity and success. Having been personally instructed by the late lamented Nitze, then by Casper, and later on by Albarrán, the present writer acquired the use of each of these instruments and has therefore no choice among

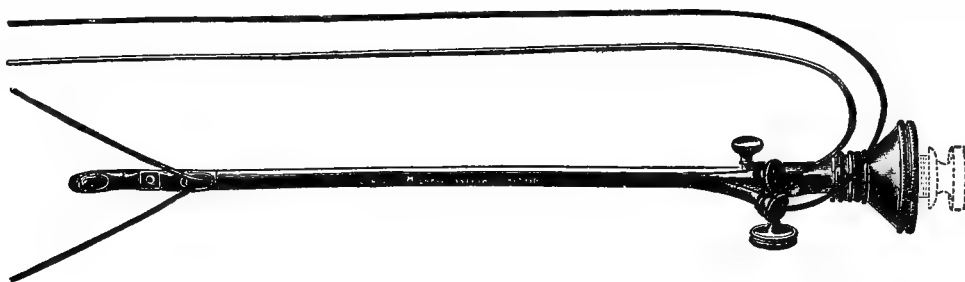


FIG. 5285.—Nitze's Instrument for Catheterizing both Ureters.

erted. As the slide is entirely removable after the ureter is penetrated, it leaves the catheter free in the ureter, bladder, and urethra. The cystoscope then can be removed, leaving the catheter to drain the kidney for

them. Personal experience makes it seem advisable that every practitioner, more particularly every genito-urinary specialist, acquire the technique as it differs for each instrument; then one or another being out of order, as is likely to happen, the examination need not be delayed by such a misadventure.

The technique of ureteral catheterism premises (1) complete familiarity with the instrument used; (2) a certain amount of manual dexterity; (3) a knowledge of the anatomy of the parts to be invaded;



FIG. 5286.—Casper's Uretercystoscope.

the time required, or to dilate a ureteral stricture by Albarrán's method.

Casper also devised a double-catheterizing cystoscope, as did Nitze, Albarrán, Schlifka, Frank, Bierhof, Schlag-

(4) a urethra that will easily permit the instrument to pass, especially the prostatic portion, without producing hemorrhage; (5) the bladder filled with a clear medium, 120 to 150 c.c. presents the average quantity which a

bladder will hold without inconvenience; ureteral catheterism is necessary sometimes, when this amount of distention cannot be obtained. Generally an adequate amount of fluid very slowly and carefully injected so expands the bladder as to permit catheterism of both ureters. The writer and his associate, Dr. Terry M. Townsend, have been obliged to catheterize ureters in bladders whose greatest capacity was apparently only 25 c.c. Gradual dilatation in most instances expanded the viscus to 50 or even 60 c.c., making ureteral catheterism, while not easy, at least possible. Willy Meyer¹⁴ places the amount of fluid necessary for vesical exploration at 90 c.c. He says: "The method usually employed by me is as follows: After gentle preliminary irrigation, the posterior urethra and bladder are anesthetized with a two-per-cent. solution of alypin. . . . I consider it superior to cocaine, as it is less poisonous, and stronger than eucaine alone or mixed with cocaine." With large experience in ureteral catheterism, the use of anesthetics becomes superfluous in the majority of cases.

The necessary conditions existing, the cystoscope carrying the ureteral catheter or catheters is introduced as described on p. 346, Vol. III. If, then, the ureteral mouths are not embedded in deep folds of mucosa, as in severe cystitis, or not covered by heavy trabeculae, nor so distorted or minute as to escape vision, they are easily brought into view.

For practice in locating the ureteral mouths and studying the inversion and distortion of cystoscopic images the writer¹⁵ devised a simple phantom, which shows the

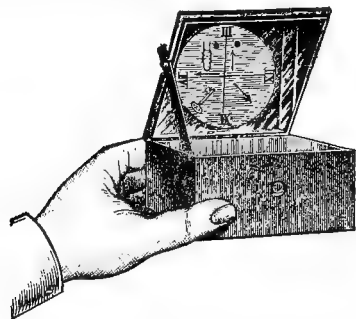


FIG. 5287.—Valentine Box-Phantom for Demonstrating and Practising Cystoscopy and Ureteral Catheterism.

normal position of the ureteral openings (Fig. 5287). Nitze honored the writer by being the first to demonstrate this device before his class in 1902.

The box phantom exhibits, when its contents are viewed through the mirror fixed at 45 degrees, a schematic representation of the base of the bladder as if seen through the cystoscope in its normal position. To impress localization upon the mind, the schematic bladder base is given a clock face, showing the left ureter at 4:30 and the right ureter at 7:30. It also has several illustrations, e.g., a hair-pin and a key in varying positions, seen inverted in the mirror. It is employed as follows: The box phantom held in the left hand, the student looks at the reflection of the schematic vesical base. With an applicator held in the right hand and inserted through the hole representing the urethra, he touches the various parts of the bladder, guided only by the reflection thereof in the mirror. A strict rule governing practice with this device is that no part of the schematic representation must be touched with the applicator, except the one intended as the objective point. To neglect this rule would be tantamount to uselessly thrusting the ureteral catheter against the vesical mucosa, thus inflicting traumatism upon it, giving the patient pain, and provoking bleedings that may obscure the dilating medium and thus thwart the purposes of the examination.

The practised eye finds no difficulty in at once discerning the interureteric fold, at each end of which a normal ureter opens. Turning the cystoscope to the right or left soon exposes the ureteral meatus. As mentioned before, it sometimes is difficult to decide, when the bladder is heavily trabeculated, which is the ureteral mouth and which the opening of an intertrabecular sulcus. Casper (*op. cit.*) says that if the region of these openings is observed for a sufficient length of time, the escaping jets of urine will show which is the ureteral mouth. At times vesical contractions may produce swirls in its contents that may so closely resemble the escaping jets of urine as to deceive the observer. Casper thinks that, in such cases, Völcker and Joseph's method of preliminary hypodermic use of indigo-carmin may be useful. It cannot, however, be recommended for this purpose, except to those whom experience has rendered very quick in catheterizing ureters, as the tinted urine soon so universally colors the vesical contents as to obscure vision. It is true, then, that attempts at catheterism may be interrupted until irrigation has again rendered the bladder contents clear, but this entails prolonging a procedure which, if not positively painful, is at least a very severe strain, especially upon the male patient. The ejaculations of normal urine from the ureter into clear bladder contents may be well studied, utilizing the comparison Nitze makes, namely, that of alcohol being squirted from a pipette into clear water.

With the ureteral meatus clearly in view, however, no difficulty is experienced in penetrating it with the catheter. The essential point to be observed is that the ureteral mouth be seen from above, as in a bird's-eye view. To accomplish this the ocular end of the cystoscope is turned to the opposite side (*i.e.*, to the right for the left ureter, and *vice versa*) and the tip of the cystoscope brought as close to the ureter as possible without touching the bladder wall. The approximation to the ureteral mouth is obtained by cautiously raising the ocular end of the cystoscope, always keeping the ureter in view, until a distinct, large image thereof is perceived.

The instrument is then firmly held with one hand, while the fingers of the other push the catheter forward. Its tip then appears, traversing the field. Another very slight projection shows whether it is in the direction of the ureteral mouth. Any deviation can be at once corrected by the screw-head near the ocular end when an instrument of the Albarrán or Nitze model is used. When a cystoscope with Casper's slide-lid is employed the necessary changes in curvature of the catheter are produced by projecting or withdrawing the slide.

When the catheter has been so curved that its tip fairly presents to the ureteral meatus, the cystoscope may be tipped slightly in the same direction. The tip of the catheter will then be seen to engage in the mouth of the ureter, especially if this little manoeuvre is performed at the instant when the ureteral mouth is open, ejecting urine. The cystoscope being still held in the same position, the catheter is again slightly projected. It will then appear as if raising a fold of mucosa. At this instant its angulation must be released, by reversing the procedure used for its curvature. The catheter may then be freely pushed throughout the length of the ureter to the renal pelvis.

The same attention may then be given the other ureter, and when its catheter is in place the cystoscope is removed. This is accomplished with the instruments of the Nitze model by pushing the catheters forward as the cystoscope is withdrawn. When the tip of the latter has reached the meatus, the projecting catheters are firmly grasped with the thumb and index finger, while the cystoscope is stripped from them. When using an instrument with the Casper slide-lid, the slide is first withdrawn, leaving the parts of the catheters which are not in the ureters lying free in the bladder; the cystoscope itself may then be withdrawn.

After the cystoscope is removed the catheters must be fastened in place. For this purpose the writer prefers the button modification of Guyon's method.¹⁵ The catheters so secured, the following important points must be determined:

1. To assure that the catheters have not been twisted during removal of the cystoscope and that consequently they are not in ureters opposite to those in which they appear to lie, it is advisable to use catheters of different colors. With this in view, it is convenient that one be of the kind marked in brown and black at intervals of one centimetre, while the other is plain. The writer makes it a rule to use the marked ("zebra") catheter for the left ureter. Then, no matter how the catheters may have become twisted in the bladder, it is known that the zebra catheter is delivering urine from the left kidney.

2. The catheter, especially when not well grasped by the ureter, may have been pulled out of this channel while removing the cystoscope. If its tip lies loosely in the bladder, there will be a continuous stream from its mouth; this is not changed by pushing the catheter in more deeply, nor by withdrawing it slightly. If it drains the renal pelvis, the discharge will be continuous, as if its tip were in the bladder. A drop of this urine examined microscopically, however, will then show the complete absence of bladder epithelia.¹⁶ If then the catheter is slightly withdrawn, the continuous flow will be replaced by the arrhythmic discharge of drops of urine. In accord with the ureteral contractions, the properly placed catheter emits from one to twelve drops of urine every ten to thirty seconds. In neurasthenics this may take the form of quite forcible ejaculations of urinary streams at even smaller intervals.

As contractions of both ureters do not occur synchronously, their urines do not escape from their respective catheters at the same time.

3. One catheter or both, though quite pervious and properly placed, may emit no urine at all. When one catheter fails, the erroneous presumption of a non-functioning kidney may be avoided by waiting, sometimes as long as half an hour. Then some warm four-per-cent. boric-acid solution may be gently injected to establish siphonage. If repeated attempts fail thus to elicit a flow from the suspected side, there is still a possibility that the catheter is of too small a calibre to occlude the ureter, and that the urine from its renal pelvis is escaping along the sides of the instrument, into the bladder. Then drainage with a larger catheter must be tried before it is decided that the kidney does not perform its function.

The interruptions of renal secretion mentioned are not infrequent, even when the kidney is perfectly healthy.

4. The first 5 or 6 c.c. of urine escaping from a catheter must be discarded, as its examination may lead to serious error. It may contain boric acid or whatever solution has been used to dilate the bladder and so yield a false specific gravity; it is furthermore likely to contain a slight admixture of blood, from the minute traumas which the catheter has inflicted upon the ureter.

These essential points determined, the patient is placed in a comfortable position, and the catheters are conducted to separate receptacles, in which the urine from each kidney may be gathered for such examination as may be necessary for precise diagnosis.

Ferd. C. Valentine.

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VALYL is the diethylamid of valerianic acid, $C_8H_{15}ON$. It is a colorless liquid with a strong valerian odor and a pungent, burning taste. It readily oxidizes when exposed to the air, and is therefore used only in the form of gelatin capsules or pearls. The capsules contain 2 grains each of valyl combined with an equal quantity of spermaceti. Valyl when brought in its pure state into contact with the mucous membrane causes a burning followed by a local irritation which does no lasting damage, however, to the membrane. It should be taken directly after meals or with milk; never on an empty stomach.

Valerian administered as an infusion (tea), tincture, or fluid extract has been employed as a domestic remedy for years, but fell into disrepute because the therapeutic principles, the esters, quickly undergo hydrolysis when brought into contact with water.

The amid of valerianic acid as above described, however, possesses the properties of valerian which have not undergone change. It has therefore the following properties of valerian as described in the older works on materia medica: it is a remedial agent in hysteria, anxiety, neurasthenia, functional disturbances of the heart, in neuralgia, hemicrania, hypochondriasis, vertigo, tinnitus, troublesome menstruation accompanied by abdominal pain and headache in climacteric troubles, and in sleeplessness from nervous disorders. It is said to be free from unpleasant by-effects, to increase the appetite, and to insure euphoria. The dose of valyl is two or three two-grain capsules or pearls two or three times a day.

John W. Wainwright.

WOLFFIAN BODY, PATHOLOGY OF.—In mammalian embryos the mesonephros or Wolffian body is a rather pyriform body symmetrically placed in the abdominal cavity. In very young embryos it is, next to the liver, the largest abdominal organ. It was first observed by Wolff in 1759. The exact origin of the Wolffian body is not yet determined; some authors hold that it is ectodermal, others that it is mesodermal, while others still ascribe to it both an ectodermal and a mesodermal origin. It is developed from the pronephric or Wolffian duct and from the mesonephric cords. The origin of the latter has not yet been wholly worked out in the case of the human body. In the lower mammals they arise through aggregations of the cells of the Wolffian ridge into solid cords which at first are not connected with the Wolffian duct or the coelomic epithelium. These cords acquire a lumen and connect at one end with the duct, while at the other end there is a condensation of the mesoderm, forming the glomeruli, into which vessels from the aorta penetrate. The tubules increase in length rapidly and in the human embryo assume an S-shape. Secondary and tertiary tubules develop in connection with each of the primary ones, but the mode and origin of these have not yet been determined, some writers hold-

ing that they arise as buds of the primary tubules, others that they have an independent origin. Through the development of these additional tubules and the progressive elongation of all the tubules, the Wolffian ridge becomes a voluminous body attached to the dorsal wall by a distinct mesentery and projecting into the coelomic cavity. Embedded in its substance on its lateral portion is the Wolffian duct; and on its mesial surface anteriorly is the developing genital ridge. In the human embryo the Wolffian body reaches its greatest development at about the sixth or seventh week, after which time it begins to degenerate. The tubules undergo retrogression and the glomeruli become occluded, so that by the sixteenth week the organ has nearly entirely disappeared. Portions of the tubules, however, persist in both sexes. In general the tubules of the Wolffian body consist of

duct representing the upper end of the Wolffian duct. Kölliker holds that the environing cells of the Graafian follicle probably arise from the Wolffian body. The excretory portion persists as the paroöphoron, a rudimentary body composed of tubules lying in the broad ligament near the tube. In about one-third of adult females remains of the Wolffian duct are found in the form of a straight tube lined by cylindrical epithelium surrounded by muscle, or of a muscle bundle without epithelium, lying anteriorly and to the side of the uterus and vagina (duct of Gärtner). According to Aichel the cortex of the suprarenals is also derived from the Wolffian body, the medullary portion coming from the sympathetic system. The origin of suprarenal tissue from the Wolffian body is made very probable from the fact that accessory suprarenal tissue (adrenals of Marchand) is

found in the broad ligament in the female, and along the spermatic cord and near the epididymis in the male.

Of the pathological conditions directly affecting the Wolffian body we know nothing at present. Hyperplasia of the primitive Wolffian body has been assumed, but not yet demonstrated. It is, however, very probable that disturbances in the development and retrogression of this organ are responsible for a number of important pathological conditions which are either apparent at birth or develop later in life. From the rudimentary structures which represent persisting portions of the Wolffian body and duct there may develop tumors of great clinical importance. Of the factors concerned immediately in the genesis and development of these tumors nothing is yet known. In general the pathological conditions which may be referred back to disturbances in the normal development and retrogression of the Wolffian body, or which have their origin in rudimentary or persisting structures derived from this organ or duct, may be classed as follows:

Malformations.—The fact that both male and female sexual organs, internal and external, develop from anlage which are at first identical makes it *a priori* very probable that disturbances in the differentiation of the sexual apparatus might be brought about through an asymmetrical development of the anlage of the right and left sides, or through the formation of organs peculiar to both sexes, or to a lack of harmony in the development of the internal and external sexual organs. The close relations between the Wolffian body and the developing sexual glands, and the part which the genital portion of the former plays in the development of the genital tract give strong support to the view that anomalies and disturbances in the development of the mesonephros are responsible, at least in part, for some of the malformations of the internal sexual apparatus. Landau and Pick have described a congenital atresia of the cervix and uterus, which they explain as due to a hyperplastic adenomyoma of mesonephric origin. Persistence of portions of the Wolffian body and duct are not infrequently found in cases of pseudohermaphroditism. In pseudohermaphroditism femininus internus such structures are found in the broad ligament and utero-vaginal wall, sometimes extending to the clitoris. At an early period of development the urogenital tract is represented by the Wolffian body, the Wolffian duct, the Müllerian duct, and the developing ovary or testis. There exists therefore at this time an indifferent stage from which the development proceeds either in one direction to become an ovary or in the other to form a testis. During this differen-

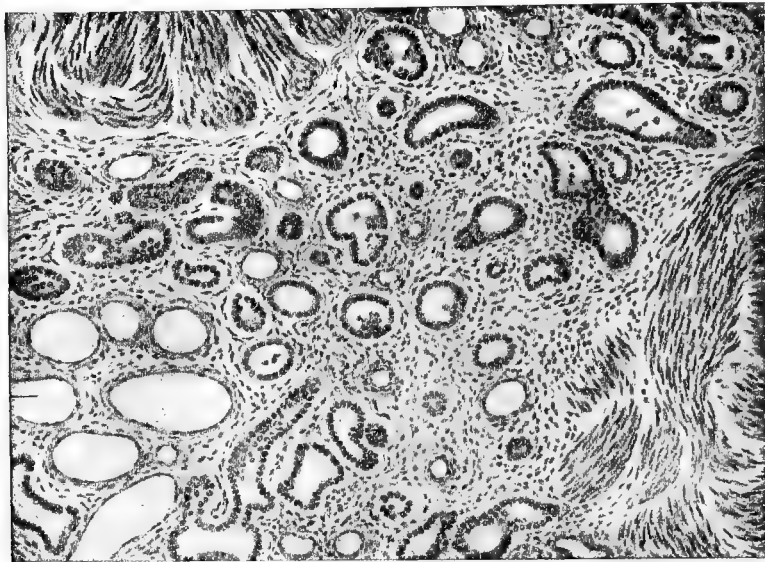


FIG. 5288.—Adenoma-like Remains of the Wolffian Body, within the Uterine Musculature (formalin, alcohol, hematoxylin, eosin). $\times 100$. (After Ziegler.)

secreting and collecting portions, the epithelium varying in the two, being low and cubical in the collecting portion and columnar in the secreting. In 1824 Jacobson discovered that the organ excreted uric acid which was carried into the allantois. He therefore called it the primordial kidney. According to Lersel the Wolffian body liberates and accumulates fatty substances in its cells. It therefore plays the part of an embryonic organ and at the same time that of an excretory organ.

In the male the upper or genital portion of the Wolffian body persists as a whole in the efferent ducts of the testis, forming the globus major of the epididymis. By some writers the seminal tubules are also regarded as arising from the Wolffian body. The excretory portion almost wholly disappears, only a small part remaining as the paroöphoron or organ of Giralès. A single elongated tubule arising from that portion of the Wolffian duct which forms the globus minor of the epididymis persists as the vas aberrans. The hydatid of Morgagni is believed by Roth to stand in close relation to the Wolffian body. The Wolffian duct is retained entire, a portion forming the body and globus minor of the epididymis, the remainder becoming converted into the vas deferens and the ejaculatory duct. In the female the genital portion of the Wolffian body persists as a group of from ten to fifteen tubules lying between the two layers of the broad ligament near the ovary, and known as the paroöphoron, or paroöphoron, or organ of Rosenmüller. Toward the ovary the tubules possess blind ends, but at the other end they are somewhat coiled and open into a collecting

tiation the Wolfian body in part undergoes degeneration and in part persists in the form of certain rudimentary organs, as already mentioned. In the male the Müllerian duct degenerates, in the female only rudiments of the Wolfian duct are preserved. Theoretically it is easily seen how disturbances of this normal differentiation of the sexual glands and ducts might arise, but the actual occurrence of such disturbances remains to be demonstrated, although pathological findings are not wanting to prove the possibility of such.

Teratomata and Dermoid Cysts.—The teratomata and dermoid cysts of the ovary and testis are believed by a number of writers to arise from the Wolfian body and duct. Bandler in particular has defended this view. He holds that in the development of the retroperitoneal dermoid cysts and the retrorectal tumors the Wolfian body, the Wolfian duct, and the caudal intestine play the important rôle. The ovarian dermoids, he believes, contain only ectodermal and mesodermal products, and these arise as the result of the displacement of ectodermal and mesodermal tissues in the formation of the Wolfian duct and Wolfian body. Regarding the duct as of ectodermal origin, and holding the view that the Wolfian body arises from the duct, he therefore regards the derivatives of the Wolfian body as ectodermal. While Bandler's views are not generally accepted (see *Teratoma*), Wilms regards the simple dermoid cysts of the retroperitoneal region and of the broad ligament, and also the mixed tumors of the cervix and vagina, as due to a displacement of ectodermal and mesodermal cells by the Wolfian duct. Von Recklinghausen found in one cyst of the ovary a formation which he regarded as resembling in structure the Wolfian body. The cysts which arise from the remains of the Wolfian body and duct found in the broad ligament, uterine wall and tubes, and also those arising in the cervix, portio vaginalis, vagina, and hymen from the duct of Gärtner may also be classed with the teratomata. Remains of the Wolfian body may also take part in the formation of the mixed tumors of the kidney. If the view that adrenal tissue is also derived from the Wolfian body be accepted the tumors (hypernephromata) arising in the kidney and elsewhere should also be classed as teratomata derived from the Wolfian body.

Tumors Derived from Wolfian Body Remains.—During the last decade much has been written upon the origin of the adenocystomata and adenomyomata of the ovary, broad ligament, tube, uterine wall, cervix, and vagina. These tumors play a rôle of great clinical importance in gynecological pathology, and in recent years much attention has been paid to their histogenesis and etiology. As a result of the discussion concerning the histogenesis of these tumors the writers upon this subject may be divided into two schools: the one affirming the origin of these growths from remains of the Wolfian body, the other holding that they arise from misplaced epithelium of Müller's duct. Some writers have compromised, in so far as the adenocystomata and adenomyomata of the uterine wall are concerned, by the hypothesis that they arise from a combination of remains of the Wolfian body and the Müllerian duct. The majority of writers, however, agree with von Recklinghausen, who holds that the adenomyomata of the uterine wall may be divided into two groups: those arising in the peripheral layers of the myometrium and those arising centrally or presenting themselves as submucosal tumors, the latter being characterized by the fact that the adenomatous portions unite to form ducts which empty into the uterine cavity. The possibility of the second group arising from the Müllerian duct is admitted. According to Neumann the intramural and subserous adenocystomata of the uterus and tubes arise most probably from embryonal remains of the Wolfian body in connection with remains of Müller's duct or from a combination of the two. The pathological glands and cyst formations found in the ovary arise from the epöphoral portion of

the Wolfian body and correspond to the medullary cords. The tumors of the tubes are of pure paroöphoral origin. The structural resemblances existing between the adenomyomata of the ovary, tubes, broad ligament, inguinal region, round ligament, and cervix, make it very probable that all of these are derived from the Wolfian body, and they may therefore be classed as mesonephric adenomyomata. The various arguments advanced in support of this view may be found in the literature cited below.

The adenosarcomata of the kidney have also been explained as arising from inclusions of portions of the Wolfian body. A similar origin has been ascribed to the adenosarcomata, adenomata, and adenocystomata of the testis and epididymis. Some writers have described glandular structures included within pelvic lymph glands, and have explained such inclusions as remains of the Wolfian body or duct. From such inclusions adenomata, cystadenomata, and carcinomata might arise.

To Aichel belongs the credit of demonstrating that adrenal tissue (cortex) is found in the closest relations with derivatives of the Wolfian body (epöphoron, paroöphoron, epididymis, paradidymis, broad ligament, etc.). From such accessory adrenal tissue (classed by Aichel as adrenals of Marchand) tumors similar to those arising from the adrenals themselves may come. Pick has reported the occurrence of a hypernephroma of the ovary, and a number of other writers have found adrenal tissue associated with adenomyomata. If the adrenals of Marchand are derived from the Wolfian body, as according to Aichel, such hypernephromata must be regarded as mesonephric.

Aldred Scott Warthin.

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Neumann: Arch. f. Gyn., Bd. 58, 1899.
Pick: Arch. f. Gyn., Bd. 57, 1898; *Ibid.*, Bd. 64, 1901.
Vassmer: Arch. f. Gyn., Bd. 64, 1901.
Von Babo: Arch. f. Gyn., Bd. 61, 1900.
Von Recklinghausen: Die Adenomyome und Cystadenome der Uterus- und Tubenwandung etc., Berlin, 1896.

WORMIAN BONES, AND FONTANELS.—Wormian bones are small bones varying in diameter from 1 or 2 mm. to more than 20 mm. They are to be found ordinarily at the angles of the sutures of the cranium, and particularly in the lambdoid sutures (Fig. 5248). They take the name of Wormian bones from Claus Wormius, a physician of Copenhagen, who first gave a detailed description of them, though an account of them had been given before by Gæthe.

The Wormian bones are regarded by some writers as evidence of retarded ossification, while by others they are considered to indicate excessive ossification. Doubtless both theories are true. In some instances the usual centres of ossification do not go on to the full development, and the coalescence which occurs in the formation of a perfect bone fails to take place; this is probably what happens in the case of the largest Wormian bones, which are found in the fontanels.

According to Meckel, isolated osseous germs develop



FIG. 5289.—Wormian Bones. (After Broca.)

at the circumference of the occipital bone and unite themselves with it. Sometimes, though rarely, thicker ones develop about the articular regions. When there is an arrest of evolution of one or more of these inferior centres, Wormian bones are formed. Gosse, who considers Wor-

mian bones to be due to an arrest of ossification, attributes their formation to a rachitic or scrofulous condition, to the effects of violent pressure, or to hereditary transmission.

The Wormian bones which present the greatest interest are those which are occasionally found in both the

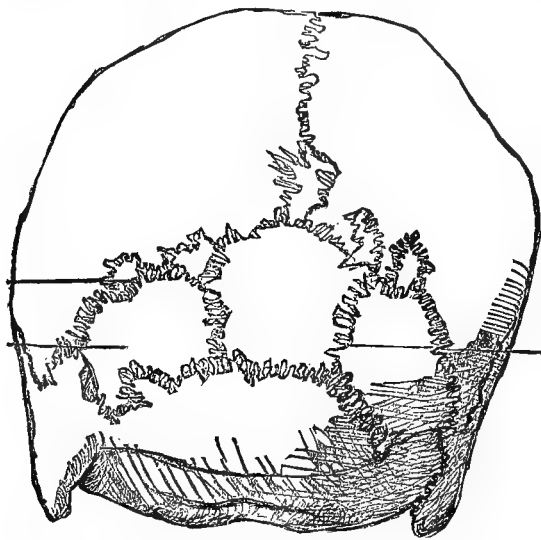


FIG. 5290.—Skull dug up in the vicinity of the Church of St. Etienne du Mont. (After Jacquot.)

anterior and posterior fontanelles. Those in the posterior fontanelles are more frequent (Figs. 5248 and 5249). A Wormian bone of large size may be confounded with the interparietal bone, which has given rise to so much ethnological discussion; a number of interesting and learned papers having been written by anthropologists upon this subject. M. Rivero and M. Tschudi, in the "*Antiquités Péruviennes*," published in 1851, gave drawings showing the bone which Anoutchune, after making studies of the skulls in various museums, announced was to be found in twenty per cent. of the Peruvian skulls. The name, "the bone of the Incas," was given to it, though,

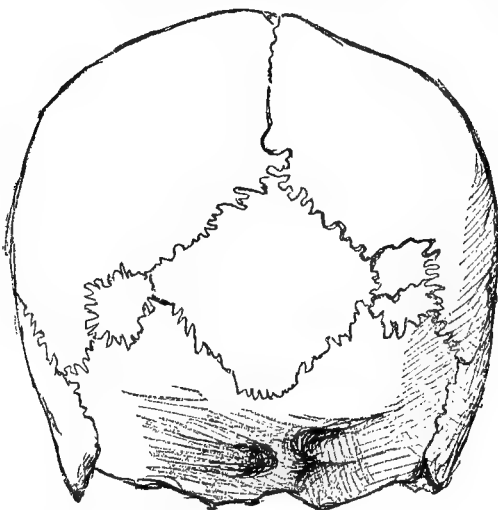


FIG. 5291.—Skull of a Negress, of Sahara. (After Jacquot.)

as Jacquot thinks, unjustly. In an elaborate paper he shows that it is found frequently in other races. The question among savants has arisen as to whether this is a mere anomaly, or a reversal to a lower type, since the

interparietal bone occurs in rodents, ruminants, dogs, and cats. The upper portion of the occipital bone develops from four osseous centres, which are separate in early foetal life, but gradually coalesce. The lateral union is accomplished first, and afterward the two segments above and below unite; when union of these two latter fails to take place, the interparietal bone is formed. The recent line of union shows very well in the skull of the new-born. Cuvier, Milne-Edwards, Geoffroy St. Hilaire, and the other writers already mentioned, insist that a distinction should be made between the interparietal bone and the large fragments occurring in the posterior fontanel, which are the true Wormian bones. Anoutchune, in his researches, made the following divisions in summing up his percentages:

1. Complete: Os Incas, or interparietal bone.
2. Incomplete: The os bi-, tri-, or quadripartitum, or, in other words, the epactal bone, os triquetrum, os quadratum.
3. Os lambdoideum.

It will therefore be seen that these bones may be single or multiple; even as many as eight having been observed by one writer quoted by Geoffroy St. Hilaire.

The effect of Wormian bones occurring in fontanelles at childbirth, and the relation which these bear to the

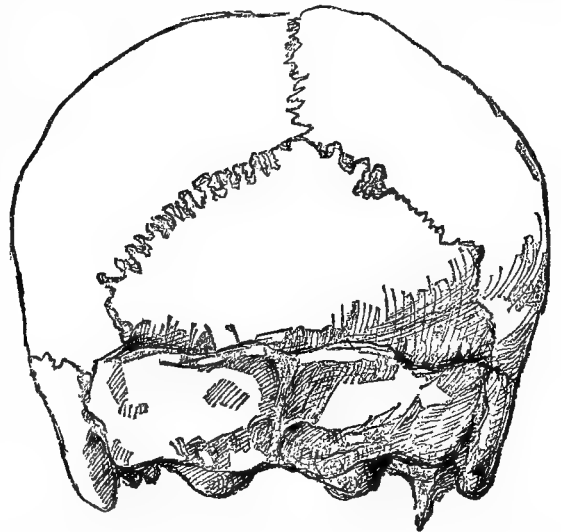


FIG. 5292.—Skull from a Breton, showing Interparietal Bone. (After Jacquot.)

moulding of the skull at that time, are questions which have received some consideration by the author of this paper.

The possibility that such bones, if of considerable size and if they occurred in the posterior fontanel, might exert a detrimental, if not fatal, influence, was suggested by three cases which came under observation at the hospital of the New York Infirmary for Women and Children. The histories of the three cases were almost identical. The mothers were all primiparæ. There was nothing abnormal in the measurements, either of the pelvises of the mothers, or of the heads of the infants. The presentations were all of them the usual left anterior occipito-iliac. The labors progressed slowly but normally through the first stage, but the second stage was very slow, lasting between two and three hours in each case. Instruments were not used in any instance, as there was a constant expectation that the labors would terminate naturally. The irregularity of the fontanel could be very easily detected. In the first two cases it gave rise to confusion in determining the position; but in the third and last case, the attendant, having had the experience with the two others, easily discovered that the posterior fontanel contained Wormian bones (Fig. 5251). Each child was still-born. The skulls of two were preserved, but

the family would not permit an autopsy to be made upon the third child, which was taken away for burial. It could, however, be easily felt that Wormian bones were

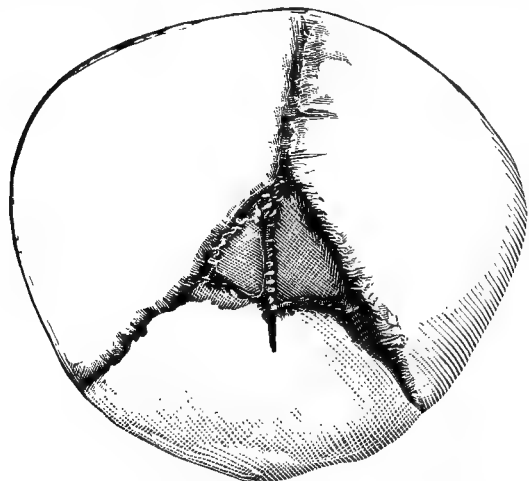


FIG. 5293.—Wormian Bones, as seen in the Author's Case.

present and that their shape and number were the same as in the other two cases, there being two triangular pieces, one larger than the other.

The writer believes it to be possible that during labor these bones may prevent the usual overlapping of the sutures of the skull, and that during the second stage—*i.e.*, when the pressure is greatest—they may even inflict serious, possibly fatal, injury upon the contents of the cranium. The question then arises, Could this be avoided by the prompt and early use of instruments? It is hoped that obstetricians will record cases of a like nature, and report upon them with a view of determining the effects produced by Wormian bones during the progress of childbirth.

Grace Peckham Murray.

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YELLOW FEVER: HISTORY AND GEOGRAPHIC DISTRIBUTION.—The geographical range of yellow fever is more restricted than that of any other acute infectious disease, and within the area of its prevalence it is essentially a disease of the littoral, and especially of seaport cities. While occasional epidemics have occurred

upon the southwest coast of the Iberian peninsula, the disease, as an epidemic, is unknown elsewhere in Europe, and there is no evidence that it has ever invaded the great and populous continent of Asia. In Africa it is limited to the west coast. In North America, although it has occasionally prevailed as an epidemic in every one of our seaport cities as far north as Boston, and in the Mississippi Valley as far north as St. Louis, it has never established itself as an endemic disease within the limits of the United States. Vera Cruz, and probably other points on the gulf coast of Mexico, are, however, at the present time, endemic foci of the disease. In South America it has prevailed as an epidemic at all of the seaports on the gulf and Atlantic coasts, as far south as Montevideo and Buenos Ayres, and on the Pacific along the coast of Peru.

The region in which the disease has had the greatest and most frequent prevalence is bounded by the shores of the Gulf of Mexico, and includes the West India islands. Within the past few years yellow fever has been carried to the west coast of North America, and has prevailed as an epidemic as far north as the Mexican port of Guaymas, on the Gulf of California.

The idea that yellow fever may originate *de novo*, within the area of its occasional prevalence, was entertained by many medical authors during the first half of the past century. Thus Cornillac (1886) says: "In the zone which is habitual to it, yellow fever may develop at a given moment without apparent cause. It is born spontaneously at a point of this zone, or at several at a time, and neither the temperature, moisture, barometric pressure, electricity, nor finally effluvia given off from the soil, can explain this sudden invasion." It is true that, in localities where the disease is endemic, cases occur which are not directly traceable to importation, but it is also true that in the principal endemic foci of the disease, such as Vera Cruz, Havana, and Rio Janeiro, yellow fever was at one time unknown, and we have reliable historical data fixing the date of its importation. In short, a careful consideration of the historical evidence relating to the disease gives no support to the idea of independent local origin, any more than in the case of smallpox, cholera, or other specific infectious diseases.

But the early history of the disease is involved in obscurity, and we are at present unable to determine whether, as maintained by some, it was endemic at certain points on the shores of the Gulf of Mexico at the time of the discovery of the "new world," or whether it was imported to the West Indies from the African coast, as maintained by others. The early historians, Herrera, Oviédo, Rochefort, and others, make reference to epidemics among the natives which occurred prior to the discovery of the Antilles, and to fatal pestilential diseases among the first settlers of these islands; but their accounts are not sufficiently exact to enable us to affirm that the disease referred to by them was yellow fever. The west coast of Africa was discovered and colonized to some extent before the discovery of America, but the first authentic accounts of the prevalence of yellow fever on this coast date back only to the year 1778, over two centuries after the first settlements had been established. On the other hand, this very epidemic of 1778 at St. Louis (Senegal) was traced to importation from Sierra Leone, a portion of the African coast which, according to Hirsch, "appears to be the headquarters of the disease, and the starting-point of its epidemic inroad into the territories lying to the north and south, as well as into the West African islands."

Rochefort, whose "Histoire naturelle et morale des îles Antilles de l'Amérique" was published in Holland in 1558, says of the West Indies: "The air of all those islands is very temperate, and healthy when one is accustomed to it. The *peste* was formerly unknown there as well as in China and other places in the Orient; but some years since the islands were afflicted with malignant fevers, which the physicians considered contagious. The bad air was brought there by some ships which came from the coast of Africa, but at present we hear nothing more of these maladies."

It seems very probable that a pestilential malady which prevailed for a time in these usually healthy islands and then disappeared was in fact yellow fever, and that it was introduced by ships from the west coast of Africa is not at all incredible. Indeed, it almost seems necessary to look for an original endemic focus of the disease outside of the West Indies, for the reason that, in the comparatively few places where it is now endemic, there is historical evidence to show that there was a first importation and a previous period of exemption; while, on the other hand, the conditions upon which endemicity at the present day seems mainly to depend were formerly unknown—conditions arising from the aggregation of population at seaport cities, as at Havana, Vera Cruz, and Rio Janeiro.

Some authors have attempted to identify the epidemic disease mentioned by Humboldt—called by the natives "Matlazahuatl"—which prevailed in Mexico in 1545, 1576, 1736-37, and 1761-62, with yellow fever; but, as pointed out by Hirsch, this disease prevailed almost exclusively among the natives of the interior and of the tableland of Mexico, while yellow fever is essentially a disease of the littoral.

Cornillac, a French author who has made a careful study of the sanitary history of the West Indies, as contained in the works of Oviédo, Herrera, Gomara, and other Spanish authors of the sixteenth century, arrives at the conclusion that the pestilential disease from which the settlers in the first Spanish colony at Nueva-Isabella, and at Santo Domingo (1494-1514), are said to have suffered, and which was characterized by a "saffron-yellow" color of the skin, was in truth yellow fever. While it appears quite probable that this was so, we cannot accept it as demonstrated, as the first authentic accounts of yellow fever in the West Indies date from about the middle of the following century.

In 1635 a French colony was established upon the island of Guadeloupe, and shortly after their arrival a pestilential disease appeared among the colonists which, from the account given by Dutertre, a Catholic priest who came to the island five years later, is accepted by Hirsch and by Cornillac as having been yellow fever. From Dutertre's account, however, as quoted by Cornillac, it would appear that yellow fever was first imported into the island of Guadeloupe in the year 1648, and that the great mortality previously reported was due to other causes. Dutertre says: "During this same year 1648, the *peste*, until then unknown in these islands since they were inhabited by the French, was brought there by some vessels. It commenced at Saint-Christophe, and during the eighteen months that it lasted carried away nearly one-third of the inhabitants. This epidemic *peste* caused in those who were attacked a violent *mal de tête*, great debility in all the members, and continual vomiting, so that in three days it put a man in his tomb. This contagious malady was brought to Guadeloupe by a ship from La Rochelle, called *Le Bœuf*."

At Barbadoes the disease may have prevailed for some years prior to its introduction into Guadeloupe, but the first authentic account relates to the year 1647. Richard Ligon, who arrived at the island in the month of September of this year, says that the city of Barbadoes was at that time suffering from a scourge which caused great ravages, so that the living scarcely sufficed to bury the dead. According to this author, the cause of the epidemic was unknown; it was uncertain whether it had been imported, or whether it originated from bad food, the use of marsh water, and the intemperance of the colonists. Ligon inclines to attribute it largely to the latter cause, and remarks that not more than one woman died for every ten men. We may safely assume, from the subsequent history of the island of Barbadoes, that the epidemic plague referred to by Ligon was not of local origin, for, with a rapidly increasing population this island has enjoyed considerable periods of immunity from yellow fever, and when epidemics have occurred they have, as a rule, been clearly traced to importation. From this time—1647-48—the history of yellow fever in

the West Indies is a history of epidemic outbreaks at varying intervals, at the principal seaport towns, traced sometimes to importation, but more commonly assumed to be of local origin. It was epidemic in Jamaica in 1655, and again in 1671; at Santo Domingo in 1656; at Martinique in 1688 and 1696. In 1699 it prevailed widely as an epidemic in the West Indies, and, according to Hinemann, made its first appearance at Vera Cruz, the principal seaport on the gulf coast of Mexico.

CUBA.—I cannot attempt to follow here the history of yellow fever in the West Indies generally, but shall give an account of its prevalence in Havana.

The historian Pezuela records the prevalence of a malignant pestilential disease in Havana in 1648, a year in which, as we have seen, yellow fever was epidemic in the islands of Guadeloupe and of Barbadoes. He says: "In this year there occurred in Havana a great pest of putrid fevers which remained in the port almost all the summer. A large part of the garrison and a larger part of the crew and passengers in the vessels died." The epidemic continued the following year, and in 1653-54, according to the author above quoted, "the epidemic was renewed with equal fury"; and in 1655 "in the capital continued to carry away its victims without regard to rivalries and passions." According to Dr. S. E. Chaillé, president of the Havana Yellow-fever Commission (1879), from whose report we have quoted the above extracts from Pezuela, there is no historical evidence of the prevalence of yellow fever in Havana for more than a hundred years after the date mentioned. "On the contrary, there are repeated records of the great salubrity of the climate and the absence of epidemic diseases."

It was not until the year 1761 that yellow fever established itself in the previously healthy city. Pezuela gives the following account of its introduction: "Although Havana is situated on the northern boundary of the torrid zone, it was very justly considered one of the most healthy localities on the island before its invasion, in a permanent manner, by the *vomito negro*, imported from Vera Cruz in the summer of 1761. . . . In May there came from Vera Cruz, with materials and some prisoners destined for the works on the exterior fortifications of Havana, the men-of-war *Reina* and *America*, which communicated to the neighborhood the epidemic known by the name of 'vomito negro.' At the end of the following June there were stationed in this port nine men-of-war, despatched from Cadiz, and sent to the chief of the squadron, Don Entienne de Hevia; they brought a reinforcement of 2,000 men. More than 3,000 persons succumbed to the epidemic on this the *first appearance* of the vomito."

From this time the new levies of troops sent from Spain to Cuba continued to suffer enormous losses from the endemic pestilence. In 1779 there arrived from Spain, then at war with Great Britain, "an army of 3,500 men, which was immediately decimated by the vomito." In 1780, during the month of August, an army of 8,000 men was landed in Havana, which during the two following months suffered a loss of about 2,000 men with the vomito. Pezuela records the fact that in 1794, in the garrison and squadron, there were more than 1,600 victims to the disease.

The endemicity of yellow fever in Havana was fully established by the researches of the commission sent to that city in 1879, by the National Board of Health. Dr. Chaillé, president of this commission, says in his elaborate report, published in 1881: "Since 1761 yellow fever has prevailed certainly in Havana, and probably in other places in Cuba, every year, and the dates of prevalence recorded in our text-books indicate no more than the years of greatest prevalence. The disease prevails in Havana, and in some other places in Cuba, not only every year, but also every month in the year; records in 1837 indicate that at that date the monthly prevalence had become habitual in Havana; the statistics, solely of the military and civil hospitals, prove that during the 408 months, 1846-79, there was only one

single month free from officially recorded cases of yellow fever."

The following tables are from the "Preliminary Report of the Havana Yellow-fever Commission".

MONTHLY MAXIMUM AND MINIMUM DEATHS BY YELLOW FEVER IN HAVANA DURING THE TEN YEARS 1870-79.

Months.	Minim.	Maxim.	Months.	Minim.	Maxim.
January	6	32	July	68	675
February	4	24	August	70	416
March	4	32	September	35	234
April	4	37	October	28	185
May	13	103	November	5	150
June	66	378	December	9	82

In no one of the ten years 1870-79 have there ever been fewer deaths than in the first, nor more than in the second, column, and the total deaths by yellow fever for each year were as follows:

TOTAL DEATHS BY YELLOW FEVER IN HAVANA.

In 1870	665	In 1875	1,001
In 1871	991	In 1876	1,619
In 1872	515	In 1877	1,374
In 1873	1,244	In 1878	1,559
In 1874	1,425	In 1879, to Oct. 1st..	1,353

The disease continued to prevail in Havana up to the time of the occupation of that city by the United States troops in 1898. According to Colonel Gorgas the mortality during the month of October between the years 1889 and 1899 ranged from 25 in 1899 to 240 in 1896 (average for ten years 64.27). After the demonstration by Major Reed and his associates (1900) that yellow fever is transmitted through the agency of mosquitoes, Colonel Gorgas (then Major Gorgas, surgeon U.S.A.) inaugurated his successful campaign against infected mosquitoes, and in November, 1901, was able to report that: "During the month we have had no cases and no deaths from yellow fever. Last year, 1900, we had during this month 214 cases and 54 deaths. This year the last case occurred on September 28th, that is, we have gone over two months without a single case or death belonging to Havana." This record has been continued since, and the city of Havana has ceased to be one of the endemic foci of the disease under consideration.

The board for the study of yellow fever in the island of Cuba was appointed upon my recommendation and received its instructions from me. It was constituted as follows: Major Walter Reed, surgeon U.S.A., Dr. James Carroll, contract surgeon U.S.A. (now assistant surgeon U.S.A.), Dr. A. Agramonte, contract surgeon U.S.A., and Dr. Jesse W. Lazear, contract surgeon U.S.A. The demonstration that yellow fever is transmitted by infected mosquitoes was made during the summer of 1900 and announced in a "Preliminary Note" read at the meeting of the American Public Health Association, October 22d, 1900. The conclusions of this board have been fully confirmed by the commission sent by the French Government in 1901 to investigate yellow fever in Rio Janeiro. This commission found that the blood serum of yellow-fever patients is virulent up to the third day of the disease, but not later. The virus passes with the serum through a Chamberlain filter (bougie F). This is in accord with the results obtained by Major Reed and his associates, who found that blood serum from a yellow-fever patient, obtained during the first three days of the disease, when passed through a Berkefeld filter still contains the specific infectious agent, as proved by successful inoculations in susceptible individuals.

These results are in accord with my own conclusions, reached after extended investigations made in Cuba, in Brazil, and in Mexico (in 1878, 1887, 1888, and 1889). In my final report I say:

"The specific cause of yellow fever has not yet been demonstrated.

"It is demonstrated that micro-organisms capable of

development in the culture media usually employed by bacteriologists, are only found in the blood and tissues of yellow-fever cadavers in exceptional cases, when cultures are made very soon after death."

The inference from filtration experiments considered in connection with the fact that it has not been possible to demonstrate the presence of a specific micro-organism in the virulent blood of yellow-fever patients appears to be that the germ of yellow fever is so minute as to be ultra-microscopic.

Yellow fever prevailed almost annually in some of the other seaports of the island of Cuba prior to the American occupation of that island, especially in Matanzas, Cienfuegos, Santiago de Cuba, and Manzanillo.

Vera Cruz, the principal seaport on the gulf coast of Mexico, is also the principal endemic focus of yellow fever upon this coast. According to Hinemann, the first epidemic occurred in 1699, a year in which yellow fever was widely prevalent in the West Indies, and in which it prevailed for the first time as an epidemic in the city of Philadelphia.

The following table, which I copy from a paper by Dr. Zacarias R. Molina, a medical officer of the Mexican army who has for a number of years been on duty in the Military Hospital at Vera Cruz, shows the continued prevalence of the disease in that city during a period of nearly fifteen years:

MORTALITY FROM YELLOW FEVER IN THE CITY OF VERA CRUZ FROM JULY, 1867, TO DECEMBER, 1881.

Months.	1867.	1868.	1869.	1870.	1871.	1872.	1873.	1874.	1875.	1876.	1877.	1878.	1879.	1880.	1881.
January...	..	7	3	2	1	1	7	16	6	2	28
February...	..	6	2	..	2	2	1	1	5	4	..	22
March	7	1	4	4	1	2	1	29
April	31	2	..	0	5	3	..	11	1	1	1	29
May	42	19	14	1	2	29	..	4	7	1	..	94
June	16	113	45	19	3	93	2	7	58	1	..	233
July	8	28	1	..	71	53	59	11	118	4	54	114	2	1	132
August	29	21	1	..	17	39	59	24	105	7	144	110	1	3	39
September ..	36	21	10	29	74	7	41	9	164	62	3	..	22
October	17	9	1	3	15	11	20	12	13	6	77	45	..	42	25
November	11	2	2	5	2	..	10	11	2	1	50	24	..	92	18
December ..	8	3	..	2	4	6	7	6	..	3	27	7	..	98	4
Totals...	109	193	7	10	271	210	223	79	425	34	528	444	21	249	675

There is no evidence of continued prevalence at other towns upon the Mexican Coast, but epidemics, which have usually been traced to importation from Vera Cruz, have occurred at *Matamoros*, at *Tampico*, at *Turpan*, at *Campêche*, and at *Manzanillo*.

The gulf coast of South America, and especially the English and French settlements in Guiana, have been frequently visited by epidemics of yellow fever, and it is probable that the disease is endemic at one or more points upon this coast. Its epidemic prevalence is recorded for the following years at *Demerara*: 1793-96, 1800, 1803, 1818, 1819, 1820, 1821, 1825, 1827, 1828, 1831, 1837-39, 1841-45, 1851-53, 1861-66 (Hirsch).

In Venezuela the disease has prevailed at the capital, *Caracas*, and the neighboring seaport, *La Guayra*.

In Central America epidemics have occurred at all of the principal seaports: *Panama*, *Portobello*, *Belize*, *Nicaragua*.

BRAZIL.—The Portuguese author El hastião da Rocha Pitti has given an account, in his "History of Portuguese America," published in Lisbon in the year 1730, of an epidemic malady which prevailed in Pernambuco in the year 1686, which very probably was yellow fever. This author says (Book VII., p. 427 *et seq.*): "In the year 1686, commenced in Pernambuco that terrible plague (contagious disease, *Bicha*) which must be attributed to the sins of the population of these provinces, corrupted by the vices into which they were enticed by the wealth and freedom of Brazil. Many causes are alleged, the most worthy of attention being the arrival of some barrels of meat which returned from the island of São Thomé (St. Thomas). These were opened by a cooper,

who shortly afterward fell dead. Soon after several persons of his family, to whom he had communicated the disease, also died. The epidemic spread to such an extent among the inhabitants of Recife (Pernambuco) that the mortality exceeded two thousand, which was very large in proportion to the population. Thence the disease extended to Olinda and its vicinity, and very few were the persons who escaped it, such were its virulence and intensity." The account given by the historian of the clinical features of this pestilential disease is, of course, very imperfect, but it seems to justify the belief that the disease was really yellow fever.

The highest medical authorities in Brazil agree that yellow fever was not endemic in the principal seaports of the empire prior to the year 1849, when it was introduced into the city of Bahia by the North American brig *Brazil*, which sailed from New Orleans, where yellow fever was prevailing, and touched at Havana. Two of the crew of this brig died of yellow fever during her voyage from the latter port to Bahia. Soon after her arrival the disease made its appearance among those who had communicated with the ship, and later on other vessels in the harbor. The first case occurred a few days after the arrival of this brig (November 3d). A part of her cargo is said to have consisted of little barrels of beef which had become putrid. From Bahia the disease was carried to Rio Janeiro, where during the epidemic season of 1850 it caused a mortality of 4,160.

According to Professor Barata, of the Faculty of Medicine of Rio Janeiro, yellow fever continued to prevail in Brazil until the year 1861, when it disappeared for eight years, to reappear in 1869-70, as the result of a fresh importation. The Italian ship *Creolla del Plata*, which had touched at St. Iago, where yellow fever was prevailing, is named as the vessel which introduced the disease on this occasion.

The mortality from the disease under consideration in the city of Rio from the time of its introduction in 1850 to the year 1886, is shown by the following table:

Mortality.	Mortality.
1850.....4,160	1869.....274
1851.....475	1870.....1,117
1852.....1,943	1871.....8
1853.....853	1872.....102
1854.....21	1873.....3,659
1855.....0	1874.....829
1856.....0	1875.....1,292
1857.....1,425	1876.....3,317
1858.....800	1877.....282
1859.....500	1878.....1,174
1860.....1,249	1879.....974
1861.....247	1880.....1,433
1862.....12	1881.....219
1863.....0	1882.....95
1864.....0	1883.....1,336
1865.....0	1884.....618
1866.....0	1885.....278
1867.....0	1886.....1,397
1868.....0	

In 1855 yellow fever is said, by Hirsch, to have prevailed extensively in Brazil, although this was not an epidemic year in Rio Janeiro. The following year it extended along the Amazon far into the interior of the country. The years of greatest epidemic prevalence since that date have been 1859-60, 1862, 1869-70, 1872-73, 1875-77 (Hirsch).

From Brazilian ports the disease has occasionally been introduced into the cities at the mouth of the Rio de la Plata, and has there caused great loss of life. The first epidemic at Montevideo was in 1857, and it was again introduced into this city, from Pernambuco, in 1872. It prevailed in the city of Buenos Ayres in 1858 and in 1870.

Yellow fever is said to have been conveyed to the Pacific coast of South America by a party of German emigrants, who landed at Callao, Peru, in 1854. The disease spread from this port to the capital, and in the course of the next two or three years to the principal towns upon the Peruvian coast, where it continued to prevail up to the year 1869.

Chili, up to the present time, has remained exempt from the disease (Hirsch).

Upon the *West Coast of Africa* the headquarters of yellow fever is that portion of the coast which belongs to the province of *Sierra Leone*, and epidemics at other points upon the African coast have frequently been traced to this locality. It seems very doubtful, however, whether, as some authors suppose, this is really the original source of the disease. The French authors Béranger-Feraud and Bourru both call attention to the fact that we have no account of the disease prior to the year 1778, although the African coast was discovered and colonized long before the discovery of the West Indies; and that, on the other hand, the early settlers in these islands suffered from a pestilential malady which very probably was yellow fever.

At *St. Louis* (Senegal) an epidemic occurred in 1778, and this is the first outbreak of the disease of which we have any reliable information in this portion of the world. The disease in this instance is said by Schotte to have been imported from *Sierra Leone*, where epidemics are recorded to have occurred during the past century in 1816, 1823, 1825, 1829-30, 1837-39, 1845-47, 1859, 1862, 1864, 1865-66, 1868, 1878 (?) (Hirsch). Frequent epidemics have also occurred at *Senegambia*, and the disease has prevailed upon the *Gold Coast* (1852, 1857, 1862), the *Congo Coast* (1816, 1860, 1862, 1865), at the *Cape Verde Islands* (1845, 1862, 1868), and the *Canary Islands* (1701, 1771, 1810, 1846, 1862).

In Europe the ravages of yellow fever have been restricted mainly to the Iberian peninsula. This is due, no doubt, to the frequent intercourse between Spain and Portugal and the West Indian ports, in which the disease is most prevalent, and to the fact that the summer temperature of these countries is favorable for the epidemic extension of the disease; whereas the more northern portions of Europe are practically outside of the yellow-fever zone.

The first epidemic in *Spain* occurred in the year 1700, at Cadiz. This city also suffered in 1730-31, 1733-34, 1764, 1780, 1800, 1804, 1810, 1819-21. The epidemics of 1800, 1810, and 1819 were not limited to the city of Cadiz, but the disease extended to the interior and caused a considerable loss of life in the provinces of Granada and Andalusia, and also in some of the towns of Murcia and Catalonia—especially in Barcelona, from which city the disease was conveyed to the island of Majorca during the last epidemic. No widespread epidemic has occurred in Spain since 1821, but local outbreaks, as a result of importation from the West Indies, have occurred in Gibraltar (1828), Barcelona (1870), and Madrid (1878).

The first epidemic at *Lisbon* was in 1723, a second was inaugurated in 1856, and during the following year developed into a devastating scourge which extended to the towns of Belem, Olivaes, and Almada.

In *Italy* yellow fever has only once effected a temporary lodgment—at Leghorn, in 1804, into which city it was imported from Spain.

Ships with yellow fever on board have occasionally arrived at English and French ports, but local conditions have apparently not been favorable to an extension of the disease, except to a limited extent at Brest, in 1856, at St. Nazaire, in 1861, and at Swansea (Wales), in 1864.

Bahama Islands.—Yellow fever prevailed as an epidemic at Nassau in 1861, 1862, 1863, and in 1869.

According to Hirsch, yellow fever prevailed, to a limited extent, at Halifax (latitude 44° 26'), in 1861, and at Quebec (latitude 46° 50'), in 1805.

PREVALENCE OF YELLOW FEVER IN THE UNITED STATES.—*New Hampshire*.—Portsmouth is the most northern point in the United States which has suffered an epidemic of yellow fever. In 1798, and again in 1802, during which year the disease was epidemic in New York and in Philadelphia, it was also epidemic in this city.

Massachusetts.—In 1693 an English expedition sailed from Boston for the purpose of taking from the French the island of Martinique. The expedition failed in its object and returned to Boston on June 17th, with yellow fever on board the vessels of the fleet. Hutchinson, in

his "History of Massachusetts Bay," says the mortality among the sailors had been 1,300, out of a total strength of 2,100, and that out of the same number of soldiers the loss was 1,800. He states that the disease spread from the fleet to the town, and that many families left town and resided in the country until the infection had ceased. This is the first authentic account of the occurrence of yellow fever within the present limits of the United States. In 1796 the disease prevailed to a limited extent in Boston and in Newburyport. In 1798 it prevailed as an epidemic in Boston, where the mortality was 200, and, in 1802, 60 fatal cases occurred in the same city. Some cases also occurred in the years 1800, 1819, and 1858.

Rhode Island.—The city of Providence was several times visited by yellow fever during the latter part of the eighteenth and the beginning of the last century—1794, 1795 (mortality 45), 1797 (mortality 45), 1800, 1805. The disease prevailed at Newport in 1798, and at Bristol in 1797.

Connecticut.—The disease prevailed at New London in 1795, and again in 1798, when the mortality was 81. Hirsch records the occurrence of the disease at New Haven in 1743, 1794, and 1805; at Middletown in 1820; at Chatham in 1796, and at Hartford in 1799.

New York.—Epidemics of greater or less extent have occurred in New York City and its immediate vicinity in 1693, 1702, 1743 (mortality 217), 1745, 1762, 1791, 1794, 1795 (mortality 730), 1798 (mortality 2,080), 1799 (mortality 76), 1800, 1801, 1803 (mortality 700), 1805 (mortality 340), 1809, 1819, 1822 (mortality 230), 1848, 1853, 1854, 1856, 1870 (mortality 49).

New Jersey.—Hirsch records the following local epidemics: Bridgetown, 1798, Chews, 1798, Woodbury, 1798, Perth Amboy, 1811.

Pennsylvania.—According to La Roche "the earliest onset of the disease occurred in 1699, when Philadelphia, then but seventeen years of age, was little more in point of extent than an ordinary country town." There are no medical accounts of this epidemic, but there is no doubt as to the nature of the disease, which caused a mortality of 220 in the new city, estimated to have contained less than four thousand inhabitants. The next epidemic in Philadelphia occurred in 1741, when the mortality was 250. Subsequent epidemics occurred in 1747, 1762, 1793 (mortality 4,041), 1794, 1797 (mortality 1,300), 1798 (mortality 3,500), 1799 (mortality 1,000), 1802 (mortality 307), 1803 (mortality 195), 1805 (mortality 400), 1819, 1820 (mortality 83), 1853 (mortality 128), 1870 (mortality 18).

Delaware.—In the epidemic of 1798 the city of Wilmington suffered a loss of 250.

Maryland.—Epidemics, for the most part of limited extent, have occurred in Baltimore in the years 1783, 1794, 1797, 1798, 1799, 1800, 1802, 1819, 1820, 1821, 1822, 1868, 1876.

Virginia.—At Norfolk epidemics are recorded as follows: 1737, 1741, 1794, 1795, 1797, 1799, 1800 (mortality 250), 1801, 1821, 1826, 1855 (mortality 1,807). An epidemic occurred at Petersburg in 1798, and at Alexandria in 1803. At Portsmouth the disease prevailed in 1852, 1854, and 1855 (mortality 1,000).

North Carolina.—Wilmington, 1796, 1800, 1821, 1862 (mortality 446); Newbern, 1799, 1864 (mortality 700); Beaufort, 1854, 1864 (mortality 68), 1871; Washington, 1800; Smithville, 1862.

South Carolina.—The first epidemic, of which we have any account, in Charleston, occurred in 1693; from this time epidemics have been numerous, and during the first half of the present century the physicians of Charleston generally considered the disease endemic in that city. That it was not seems to be demonstrated by the immunity enjoyed since 1871, an immunity which is probably due to the diminished commerce with infected ports in the West Indies, and to a more efficient quarantine service, since the fact has been recognized that the disease is not endemic.

The prevalence of yellow fever in Charleston, during the past century, is shown in the following table; recorded epidemics, prior to the year 1800, are as follows:

1693, 1699, 1700, 1703, 1728, 1732, 1734, 1739, 1745, 1748, 1753, 1755, 1761, 1762, 1768, 1770, 1792, 1794, 1795, 1796, 1797, 1798, 1799 (mortality 239). An epidemic occurred among the troops stationed at Hilton Head in 1862; Port Royal, 1877 (mortality 25).

Georgia.—At Savannah epidemics are recorded in the years 1800, 1807, 1808, 1817, 1819, 1820, 1827, 1852, 1853, 1854 (mortality 580), 1858, 1876; at St. Mary's in 1808 (mortality 84), and in 1854; at Augusta in 1839 and 1854; at Bainbridge in 1873; Brunswick, 1876, 1893.

MORTALITY FROM YELLOW FEVER IN CHARLESTON, S. C., PENSACOLA, FLA., MOBILE, ALA., NEW ORLEANS, LA., AND GALVESTON, TEXAS, DURING THE PAST CENTURY.

Year.	Charleston.	Pensacola.	Mobile.	New Orleans.	Galveston.	Year.	Charleston.	Pensacola.	Mobile.	New Orleans.	Galveston.
1800....	184	*	...	1841....	*	*	*	594	...
1801....	*	...	1842....	*	*	60	211	...
1802....	96	*	...	1843....	1	*	240	487	...
1803....	*	*	...	1844....	...	*	*	148	400
1804....	148	*	...	1845....	...	*	*	160	...
1805....	*	*	...	1846....	...	*	*	76	2,259
1806....	*	...	1847....	...	*	75	850	200
1807....	162	*	...	1848....	...	*	50	737	...
1808....	*	...	1849....	125	102	...
1809....	*	...	1850....	16	...
1810....	*	...	1851....	310	...	*	415	...
1811....	*	...	1852....	...	*	115	7,970	536
1812....	*	...	1853....	...	*	...	2,423	404
1813....	*	...	1854....	627	*	...	2,670	...
1814....	*	...	1855....	199	...
1815....	*	...	1856....	211	3,889	34*
1816....	*	...	1857....	13	*	*	182	...
1817....	272	800	...	1858....	717	*
1818....	115	...	1859....
1819....	177	...	274	2,190	...	1860....
1820....	*	...	1861....
1821....	*	...	1862....	*	*
1822....	2	257	...	239	...	1863....
1823....	1	...	1864....	*	259
1824....	235	108	...	1865....
1825....	2	*	*	49	...	1866....
1826....	5	...	1867....	34	3,093	1,150
1827....	64	*	...	109	...	1868....
1828....	26	130	...	1869....	*	587	...
1829....	130	210	...	1870....	55	...
1830....	30	117	...	1871....	213	40	...
1831....	18	...	1872....	61	27	225
1832....	2	...	1873....
1833....	95	...	1874....	...	118
1834....	49	294	...	1875....
1835....	25	5	...	1876....
1836....	442	...	1877....
1837....	350	17	...	1878....	90	600	...
1838....	351	452	250	1879....
1839....	134	...	650	3	...	1880....
1840....	22	1887....	46	290	...

* Number of deaths not stated.

Florida.—The principal seaport, Pensacola, has suffered frequent epidemics of yellow fever. Those which occurred during the past century are included in the table given above. Two epidemics are recorded as having occurred prior to the year 1800—1764 and 1765. At St. Augustine epidemics occurred in 1807, 1821, 1838, 1839, and 1841; at Key West in 1823, 1829, 1841, 1862, 1867, 1875, 1878, 1887, 1899; at Jacksonville in 1857, 1877, and 1888; at Fernandina in 1877 (mortality 498); at Tampa in 1839, 1853, 1871, 1887, 1888; at Miami, 1899.

Alabama.—The recorded epidemics in Mobile, prior to the year 1800, were in 1705, 1765, and 1766; subsequent epidemics are included in the table. Montgomery, 1853 (mortality 35), 1854 (mortality 45), 1855 (mortality 30), 1873 (mortality 102); Selma, 1853 (mortality 32); Florence, 1878.

Mississippi.—The town of Biloxi, on the gulf, has suffered from epidemics as follows: 1702, 1839, 1847, 1853, 1858, 1878, 1884, 1897; Pascagoula, 1847, 1853, 1875, 1878; Port Gibson, 1878; Shieldsborough, 1820, 1829, 1839; Port Adams, 1839, 1853; Grand Gulf, 1853; Natchez, on the Mississippi River, 1817, 1819 (mortality 180), 1823 (mortality 312), 1825 (mortality 150), 1827, 1829 (mortality 90), 1837 (mortality 230), 1839 (mortality 235), 1848, 1853, 1855, 1858; Vicksburg, 1839, 1841, 1847, 1853,

1855, 1858, 1871, 1873, 1878 (mortality 872); Jackson, 1853, 1854, 1878 (mortality 86), 1898; Holly Springs, 1878 (mortality 309); Greenville, 1878 (mortality 301); Grenada, 1878 (mortality 326); Canton, 1878 (mortality 180). Our record does not include numerous smaller places which suffered during the epidemic of 1878, Ocean Springs, 1897, Edwards, 1897.

Louisiana.—The first recorded epidemic in New Orleans was in the year 1769; other outbreaks prior to the last century were in 1791, 1793, 1794, 1795, 1796, 1797, 1799. The prevalence of the disease in this city subsequent to the year 1800 is given in the table. Baton Rouge, 1817, 1819, 1822, 1827, 1829, 1837, 1843, 1847, 1853, 1858, 1878 (mortality 193), 1898, 1899; Opelousas, 1837, 1839, 1842, 1853; St. Francisville, 1811, 1817, 1819, 1823, 1827, 1829, 1839, 1843, 1846, 1848, 1853; Shreveport, 1853, 1873 (mortality 759); Port Hudson, 1839, 1841, 1843, 1853, 1878; Thibodeaux, 1846, 1853, 1854, 1878; Washington, 1837, 1839, 1852, 1853, 1854, 1867; Morgan City, 1878 (mortality 109). Numerous smaller places during the epidemics of 1873 and of 1878; Franklin, 1898, Alexandria, 1898.

Texas.—The epidemics at Galveston are included in our table. Houston, 1839, 1844, 1847, 1848, 1853, 1854, 1858, 1859, 1864, 1867, 1870; Huntsville, 1867 (mortality 130); Hempstead, 1867 (mortality 151); Indianola, 1852, 1853, 1858, 1859, 1862, 1867 (mortality 80); La Grange, 1867 (mortality 200); Matagorda, 1862 (mortality 120); Navazota, 1867 (mortality 154); Rio Grande City, 1867 (mortality 150); Victoria, 1867 (mortality 200); Brenham, 1867 (mortality 120); Calvert, 1867 (mortality 250); Chapel Hill, 1867 (mortality 123); Columbia, 1867 (mortality 132); Brownsville, 1853, 1858, 1862, 1882; Laredo, 1903.

Tennessee.—Memphis, 1828, 1853, 1855, 1867, 1873 (mortality 1,244), 1878 (mortality 5,000), 1879 (mortality 485); Chattanooga, 1878 (mortality 135); Brownsville, 1878 (mortality 212); numerous smaller towns in 1878.

Arkansas.—Columbia, 1853; Fort Smith, 1823, Little Rock, 1873, Napoleon, 1853.

Kentucky.—Bowling Green, 1878; Hickman, 1878 (mortality 153); Louisville, 1878 (mortality 64).

Ohio.—Cincinnati, 1871, 1873, 1878 (mortality 17); Gallipolis, 1796, 1878 (mortality 18).

Illinois.—Cairo, 1873 (mortality 17), 1878 (mortality 51).

Missouri.—St. Louis, 1854, 1855, 1878 (mortality 16); New Design, 1797 (mortality 57).

Great Epidemics in the United States. 1793.—The city of Philadelphia, after enjoying an immunity from yellow fever for thirty-one years, suffered in 1793 a devastating epidemic. This epidemic, no doubt, resulted from importation, although a clear history of its introduction was not made out at the time, and the leading physicians of the city were inclined to attribute it to local origin, as a result of unsanitary conditions in connection with an unusually high temperature. La Roche says: "Dr. Rush and others laid great stress on a quantity of damaged coffee which was exposed, during the latter part of July, in a place (on a wharf and in the adjoining dock) and under circumstances which favored decomposition. Its smell was highly putrid and offensive, inasmuch that the inhabitants of the houses in Water and Front streets, who were near to it, were obliged in the hottest weather to exclude it by shutting the doors and windows. Even persons who only walked along those streets complained of intolerable fetor, which, upon inquiry, was constantly traced to the putrid coffee."

As usual, the early cases were not recognized as yellow fever. Dr. Rush says: "The report of a malignant and fatal fever being in town spread in every direction, but it did not gain universal credit. Some of those physicians who had not seen patients in it denied that any such fever existed, and asserted (though its mortality was not denied) that it was nothing but the common annual remittent of the city. Many of the citizens joined the physicians in endeavoring to discredit the account I had given of this fever, and, for a while, it was

treated with ridicule or contempt. Indignation in some instances was exerted against me." History has repeated itself, in this particular, many times in subsequent epidemics. The early cases, even in cities like New Orleans, where the physicians are well acquainted with the disease, are frequently called by some other name—"bilious fever," "pernicious fever," "malarial fever," etc.—and the physician who first ventures to name the prevailing disease "yellow fever" is treated with ridicule or with indignation.

It was not until the middle of August that a rapid succession of fatal cases convinced the physicians of the city that the fatal West Indian pestilence was again present in Philadelphia.

The presence of the disease was officially recognized on the 22d of August, when the mayor of the city gave orders for the cleaning of streets and general purification of the city. The disease continued to extend until early in October, when it reached its height. It did not cease entirely until about the 8th of November. During this short season of prevalence it caused an enormous mortality, distributed as follows: "August, 325; September, 1,442; October, 1,976; November, 118" (La Roche).

The population of the city at this time is estimated to have been a little more than 40,000, which gives a mortality of ten per cent. of the total population (total mortality 4,040). As more than 12,000 of the inhabitants fled from the city, the proportion of those who were attacked is very great. La Roche estimates the total number of cases at 11,000.

1797.—The epidemic of this year in the city of Philadelphia was less extended and less fatal. The whole number of deaths is estimated to have been about 1,300. The disease, as usual, commenced in the vicinity of the wharves (about the end of July). Unsanitary conditions, described by physicians who were witnesses of the epidemic, furnished the favorable local nidus for the exotic germ, which, according to a report of the College of Physicians of Philadelphia made in response to a request from the governor, was imported by two vessels, one from Havana and the other from Port au Prince. In this report the College of Physicians, contrary to the prevailing popular opinion and that of many prominent physicians, took the ground that the unsanitary local conditions were simply secondary or accessory causes, and recommended "a more stringent system of quarantine regulations, as the most effectual means of preventing the recurrence of the disease" (La Roche).

1798.—The epidemic of 1797 was followed the next year by a still greater one, which was not confined to the city of Philadelphia alone. The disease prevailed also in Boston (mortality 200), in Portsmouth, N. H. (mortality 100), in Newport, R. I. (mortality 2), in New London, Conn. (mortality 81), in New York (mortality 2,080), in Wilmington, Del. (mortality 250), and in Charleston, S. C. The mortality in Philadelphia was 3,645, distributed as follows: August, 626; September, 2,004; October, 943; November (from the 1st to the 5th), 72. The mortality, in proportion to the number of cases, in the city of Philadelphia, was enormous, being, according to La Roche, about as 1 to 1.27 of those attacked, or nearly eighty per cent. This is accounted for partly by the fact that the better classes of the community left the city as soon as possible after the outbreak of the disease, and the cases which occurred were consequently among the poorer classes, who inhabited the worst portions of the city. The prevailing ideas as to the treatment of fevers by depleting measures, were doubtless responsible to some extent for the excessive mortality. "The College of Physicians, faithful to the theory so long entertained by it in relation to the cause of the disease, assigned to the epidemic this year, as it had done to those of preceding seasons, a foreign origin" (La Roche).

1802.—An epidemic of smaller proportions prevailed in the year 1802, causing a mortality in Boston of 60, in Philadelphia of 307, in Wilmington of 86, in Charleston of 96. The disease also prevailed "extensively" in Baltimore, but no record of mortality is given. The preva-

lence of the disease at the seaports mentioned, especially before the time of railroad communication, is not to be ascribed to an extension from one to the others, or to "an epidemic constitution of the atmosphere"; but it doubtless occurred, for the most part, as a result of independent importation from the usual source of the disease—the West Indies. Thus we find that in 1802, while Boston and Philadelphia suffered epidemics, New York, lying between the two infected points, was free from the disease (two cases only are reported).

1853.—Passing over the minor epidemics, for the most part limited to a single city, or by coincidence merely to two or more distant seaports, we come to the epidemic of 1853, which extended through portions of the States of Florida, Alabama, Louisiana, Mississippi, Arkansas, and Texas. The towns which suffered in *Florida* were Pensacola, Milton, and Tampa. In *Alabama*, Mobile (mortality 115), Cahawba, Citronelle, Demopolis, Fulton, Hollywood, Montgomery (mortality 35), Selma (mortality 32), were the principal towns visited by the scourge. In *Louisiana* the disease prevailed at New Orleans, with a mortality of 7,970, at Alexandria, Algiers, Bay St. Louis, Bayou Sara, Centreville, Clinton, Coultierville, Franklin, Opelousas, Pattersonville, Plaquemine, Shreveport, Thibodeaux, Trenton, Washington, and various smaller places. In *Mississippi*, Biloxi, Brandon, Clinton, Grand Gulf, Greenwood, Jackson, Natchez, Pascagoula, Pass Christian, Port Gibson, Washington, Woodville, Yazoo. In *Arkansas*, Columbia, Grand Lake, Napoleon. In *Texas*, Brownsville, Cypress City, Galveston, Hockley, Houston, Indianola, Liverpool, Richmond, Saluria.

1867.—The epidemic of this year was widely extended in the State of Texas. The first recognized case in New Orleans occurred on the 10th of June. The total mortality in this city was 3,093. Other towns visited in Louisiana were New Iberia and Opelousas. In *Texas* the first cases occurred at Galveston on the 26th of June, and the total mortality in this city was 1,150. Other places visited by the epidemic were Alleyton, Anderson, Austin, Bastrop, Brenham, Calvert (mortality 250), Chapel Hill (mortality 123), Corpus Christi, Danville, Goliad, Hempstead (mortality 151), Huntsville (mortality 180), Independence, Indianola (mortality 80), La Grange (mortality 200), Liberty, Millican, Navazota (mortality 154), Oldtown, Port Lavaca, Rio Grande City (mortality 150), Victoria (mortality 200).

1873.—Florida, Alabama, Mississippi, Louisiana, and Texas again suffered from an epidemic of yellow fever in the year 1873. At Pensacola, Fla., the first recorded cases occurred August 6th, and the total mortality was 61. In *Alabama* the disease appeared at Mobile on the 21st of August, and the total mortality was but 27; Montgomery suffered a loss of 102. In *Louisiana* the mortality in the city of New Orleans was only 225, although the epidemic had its origin in this city. It was imported by the Spanish bark *Valparaiso*, which sailed from Havana, June 15th, in ballast; arrived at the New Orleans quarantine station June 24th; was detained two days, and came to the city June 26th. The first case was the mate of this vessel, who was taken sick on board July 4th, while she was lying at the wharf. But for the sickness and death of the mate of the *Valparaiso*, the origin of this epidemic would have remained obscure, and the believers in the local origin of the disease would have had a strong case, for no other cases of the disease occurred on the *Valparaiso*. This is explained by the fact that the crew consisted of acclimated Spaniards, and the mate seems to have been the only susceptible person on board who could serve as a test of the infection of the vessel at her port of departure. From New Orleans the disease was carried to Memphis by the river steamer *Bee*. It caused a mortality in this city of 2,000. River steamers from New Orleans also carried the disease to Shreveport, La., where the mortality was 759. From Shreveport a refugee fled to the town of Calvert, Texas, where he was taken sick and died; an epidemic followed with a total mortality of 125. The disease was also introduced by refugees to the town of Marshall, Texas,

where 36 deaths occurred. The epidemic of this year at Pensacola, Fla., was due to an independent importation, by the ship *Golden Dream*, and Montgomery, Ala., became infected through refugees from Pensacola.

1878.—The last extensive epidemic of yellow fever in the United States is that of 1878, which invaded 132 towns, and caused a mortality of 15,934, out of a total number of cases exceeding 74,000.

The origin of this epidemic was traced by the president of the Louisiana State Board of Health (Chopin) to the steamer *Emily B. Souder*, which arrived from Havana May 23d, and was moored at the foot of Calliope Street, New Orleans. Dr. Chopin says: "The first cases of yellow fever in New Orleans in 1878 were, undoubtedly, two of the officers of the above steamship, namely, Clarke, the purser, and Elliott, one of the engineers. Infected centres were developed in the vicinity of the houses in which these men were sick, but not until after an interval of several weeks, during which, probably owing to unfavorable conditions as to temperature, the 'germs' remained dormant, or at least multiplied so slowly as not to cause an outbreak of the disease."

Fortunately, this great epidemic has been carefully studied by a "Board of Experts, authorized by Congress," and we have a very complete history of its geographical extension, and of the deadly results which marked its course. The following data are from the report of this "Board of Experts."

Louisiana.—New Orleans mortality, 4,600; Allemands Station, 17; Baton Rouge, 193; Bayou Cypre, 7; Berwick City, 7; Buras Settlement, 3; Clinton, 15; Delhi, 34; Delta, 47; Donaldsonville, 71; Gretna, 53; Hammond, 5; Henderson, 18; Houma, 6; Jesuits Bend, 2; Labadieville, 24; La Fourche, 26; Lagonda and other plantations, 42; Morgan City, 100; Napoleonville, 8; Paincourtville, 15; Pattersonville, 47; Pilot Town, 17; Plaquemine, 125; Ponchatoula, 3; Port Eads, 13; Port Hudson, 11; St. Bernard Parish, 7; Tangipahoa, 50; Thibodeaux, 65; Teche Country plantations, 81.

Tennessee.—Bartlett, 9; Brownsville, 212; Chattanooga, 135; Colliersville, 56; Germantown, 35; Grand Junction, 74; La Grange, 37; Martin, 40; Mason, 24; Memphis, 5,000; Milan, 12; Moscow, 35; Nashville, 6 (all imported cases); Paris and suburbs, 23; Somerville, 57; White Station, 50; Williston, 11.

Alabama.—Decatur, 44; Florence, 50; Huntsville, 12; Leighton, 1; Mobile, 90; Stevenson, 6; Town Creek, 4; Tuscaloosa, 2; Tuscumbia, 31.

Mississippi.—Bay St. Louis, 82; Benton, 1; Biloxi, 45; Bolon, 34; Bovina, 7; Brown's plantations, 4; Canton, 180; Vicinity of Canton, 47; Dry Grove, 41; Friar's Point, 7; Gainesville, 2; Goodrich Landing, 12; Greenville, 301; Grenada and vicinity, 343; Horn Lake, 2; Handsboro, 16; Hernando, 80; Holly Springs, 309; Iuka, 3; Jackson, 86; Lake, 86; Lebanon, 10; Livingston, 10; McComb City, 21; Meridian, 91; Mississippi City, 15; Ocean Springs, 30; Osyka, 45; Pass Christian, 23; Pearlinton, 24; Port Gibson, 115; Country about Port Gibson, 150; Refuge Landing, 11; Rocky Springs, 38. Scranton, 20; Stoneville, 15; Spring Hill, 6; Sulphur Springs, 5; Senatobia, 7; Terrene, 4; Vicksburg, 872; Vicinity of Vicksburg, 300; Water Valley, 64; Winona, 3; Winterville and vicinity, 26; Yazoo City, 9.

Kentucky.—Bowling Green, 19; Hickman, 153; Louisville, 64 (mostly refugees).

Ohio.—Cincinnati, 17 (refugees); Gallipolis, 18.

Illinois.—Cairo, 51.

Missouri.—St. Louis, 16 (Quarantine near St. Louis).

In 1897 yellow fever again prevailed quite extensively in several of the Southern States. The epidemic had its origin at Ocean Springs, Miss. Cases occurred in 42 localities, the total number reported having been 4,325, with a mortality of 484. In Mississippi the largest number of cases occurred at Biloxi, Edwards, Scranton, and Ocean Springs; in Alabama the principal centres of infection were Mobile, Montgomery, Whistler, and Flouraton; in Louisiana New Orleans furnished by far the greater number of cases (mortality 275).

Although, in the light of our present knowledge, it would appear that the prevention of yellow fever should be a comparatively easy matter, and it has in fact been eradicated from the city of Havana, which for years was one of its principal endemic foci, a recent (1893) epidemic within the limits of the United States, at Laredo, Texas, indicates that the history of yellow fever in this country may not yet be completed. There can be no doubt, however, that the extension of this disease could be absolutely arrested if all infected individuals could be protected from the attacks of mosquitoes of the species (*S. fasciata*) which serves as an intermediate host for the parasite, or if all the infected mosquitoes could be promptly destroyed.

George M. Sternberg.

YELLOW FEVER: SYMPTOMATOLOGY, MORBID ANATOMY, TREATMENT.—DEFINITION.—Yellow fever is a communicable disease, traceable to populous centres of the littoral of the tropical Atlantic, and transmitted from man to man by the bite of the *Stegomyia* mosquito. The chief features of the disease are: (1) a fever of from two to seven days' duration, characterized by a sudden invasion and a fastigium of from one to four days' duration, followed by an irregular lysis which may be interrupted by a secondary exacerbation; (2) a steady fall of the pulse, commencing during the fastigium and leading to a remarkable slowing of the heart beat; (3) vomiting; (4) jaundice; (5) albuminuria; (6) a tendency to stasis of the circulation; and (7) to hemorrhages. The lesions consist of parenchymatous degenerations of the liver, kidney, and stomach.

GENERAL DESCRIPTION.—During the early hours of the morning the patient awakes with a slight rigor, and, on moving, experiences vertigo and numbness and heaviness of the lower extremities. This is followed by nausea, and in some instances by vomiting of the remains of the last meal; the temperature rises rapidly; frontal headache, rachialgia, and pains in the limbs develop, and the pulse becomes frequent. The face assumes an injected, turgid appearance; the eyes are red and moist. The patient looks like a person who has indulged in an alcoholic debauch. During the day the fever continues to rise and the patient complains further of discomfort, pain or burning in the epigastrium, with sensitiveness to pressure. The temperature rises to between 102° and 103° F. and the pulse to 100 or 110. After six or nine in the evening of the first day the temperature usually falls, remitting one or two degrees on the morning of the second day. After the initial elevation of the temperature the course of the disease may vary according to three different types: the descending or mild type, the continued type, and the remitting, complicated or secondary fever type. The vaso-motor erethism will begin to subside, together with the painful symptoms, after the diurnal elevation of temperature of the second day, and it is replaced either by the evidences of a gradual return to the normal, or by the signs of blood stasis with hemorrhages from the mucous membranes, or with the syndrome of a malignant icterus. The urine becomes albuminous on the second or third day of the disease. The mental attitude is usually one of alertness. Even when the patient is delirious the expression of the face is apt to be attentive, though the mind be utterly confused and the speech wild. In some cases there is somnolence. The pulse begins to fall on the second day, and continues to fall even though the temperature may rise. Recovery is usually rapid, and sequelæ are rare. Independently of the course of the temperature we may recognize certain types, such as the uncomplicated, the hemorrhagic, the icteric, the ataxic, and, as rarer forms, the anuric, the dystolic, and the fulminating. The various combinations of these, however, are of too frequent occurrence to give them any practical value. We shall find it of greater clinical import to study the symptoms in detail.

Duration.—The following table will give the duration of the fever in 275 carefully recorded cases:

Duration.	Re-covered.	Died.	Duration.	Re-covered.	Died.
Two days.....	2	0	Ten days.....	13	4
Three days.....	5	1	Eleven days....	3	1
Four days.....	7	4	Twelve days....	6	0
Five days.....	25	2	Thirteen days..	6	1
Six days.....	39	16	Fourteen days..	2	1
Seven days.....	56	13	Fifteen days....	1	1
Eight days.....	27	7	Twenty days....	0	1
Nine days.....	19	11	Twenty-three days.....	1	0

From the above table it will be seen that the duration of the cases that end in recovery is, in the majority of instances, seven days; and that fatal cases are more apt to terminate on the sixth day. Cases of more than ten days' duration are comparatively rare.

Temperature.—In the classical descriptions of yellow fever, dating from the period before the thermometer came into general use, we find it stated that a remission, occurring about the third day of the disease, is a prominent feature of the thermic curve of yellow fever. Some authors speak of this disease as a fever of two paroxysms separated by the so-called period of calm. If we disregard the readings of the thermometer we frequently are impressed with the accuracy of this description. As the vascular erethism of the period of invasion subsides, there is a marked change in the appearance of the patient. In grave cases there is a tendency to stasis; at the same time internal hemorrhages may be setting in. Hence the extremities become cold. Especially about the wrists we observe coolness of the surface with or without moisture. But all this does not coincide necessarily with a fall of the internal temperature. In yellow fever, as in other diseases in which definite lesions of an acute character set in during the first week, oscillations of the temperature, remissions, secondary fevers occur with more or less frequency. We are, therefore, not surprised to find that temperature charts of plague, scarlet fever, variola, and measles, resemble very closely those of yellow fever. The tropical form of malaria, in

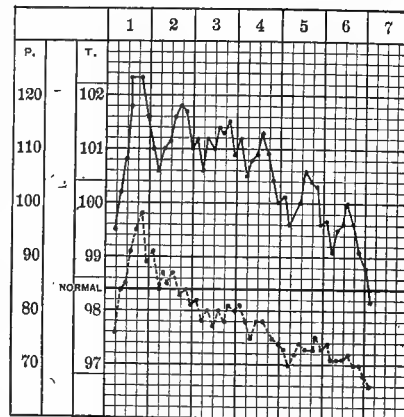


FIG. 5294.—Composite Chart of Eighty Cases of Yellow Fever, all Ending Favorably on the Seventh Day. Temperature, —; pulse,

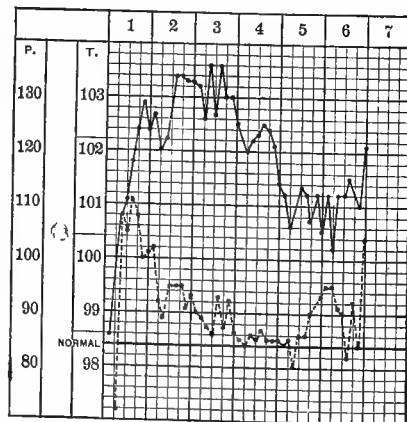


FIG. 5295.—Composite Chart of Twenty Cases of Yellow Fever, all Ending Fatally on the Sixth Day.

its primary manifestations, also frequently resembles the remitting type of yellow fever.

I have decided to present two composite charts of yellow fever. Such charts are usually of little value because the averages are obtained from cases that vary as to their intensity, their duration, and their termination. But with the large material at my disposal, I have been able to present two groups of the most common class of cases, namely, the cases terminating favorably on the seventh day, or morning of the eighth, and those terminating fatally on the sixth day (see Figs. 5294 and 5295).

As stated in the general description of the disease three types of thermic curve are found in yellow fever:

1st. *The Descending Type.*—It is usually mild. It is described by Finlay under the name of abortive type. It represents the inflammatory fever and the acclimating fever of creole physicians. The temperature reaches its acme on the evening of the first or second day, and descends in two, three, or four days through a

down-grade series of oscillations. Occasionally such cases may end fatally on the third or fourth day without a secondary rise (see Figs. 5296 and 5297).

Remitting Type.—Usually severe. Many of the fatal cases present a secondary rise of the temperature which generally follows a depression caused by hemorrhage. The persistency of the hemorrhage may cause a second depression followed by a third rise of the temperature. Many cases of the remitting type end in recovery, and some may be quite mild (see Fig. 5298).

It will be observed in Fig. 5299 that the remission occurs during the first night of the disease. This case is

one of the experimental cases inoculated by mosquitoes at Las Animas Hospital in Havana. This early remission is certainly not the remission referred to in the classical descriptions of the disease. Other observers have not had the opportunity given us by the experimental cases to study the development of the fever during the first twenty-four hours. Now, this early remission, heretofore undescribed, occurs in quite a number of cases, and is, to me, a more striking phenomenon than the later remission so much insisted upon by many authorities (see Fig. 5299).

Continued Type.—Usually fatal. The temperature need not be very high, but it is maintained at the same level for several days with very small oscillations. The black vomit will appear late in the disease, when the fall of the temperature is well established, showing the relation that exists between the two symptoms. These cases are apt to terminate with uræmic

The diurnal oscillations of the temperature vary considerably, conforming in general with the normal type; the minimum is reached about 6 A.M., and the maximum between 3 and 6 P.M. A rapid rise or fall may present itself at irregular hours, but a regular *typhus inversus* is rarely met with.

The Pulse.—In the stage of invasion, and during the first and, perhaps, the second day of the disease, the pulse is similar to that of other acute febrile diseases. It is large, bounding, and frequent in proportion to the elevation of the temperature. But during the second or third day the frequency of the pulse diminishes, and may continue to drop until very slow readings are reached at the time of the deferescence. The fall of the pulse does not follow upon a corresponding fall of the temperature. The body heat, in fact, may rise or may continue at the same level while the pulse is falling. This deviation from the usual correlation between the temperature and the pulse constitutes

one of the most characteristic features of the disease. The temperature and pulse charts that have been selected for this paper illustrate the point in question. Even when the general trend of the pulse line does not conform with the type I am describing, it will be noticed that at some time in the course of the disease, be it only for a few hours, a falling pulse will coincide with a rising temperature. It is quite rare to find a chart of yellow fever in which at least an occasional manifestation of this phenomenon does not show itself.

The pulse on the first day will rise to about 110. In the descending type of temperature the pulse will rapidly fall and may reach 45 or 50 with the deferescence. If there be a secondary rise of the temperature the pulse may be but slightly, or not at all, affected by it. In fatal cases, however, the pulse will become frequent in the last stages of the disease, and it is quite common to find under these circumstances a gradual or sudden fall of the temperature with a progressive elevation of the pulse—a symptom of very grave import.

The relatively slow heart beat in complicated cases, during the secondary rise of the temperature, may be deceptive to the inexperienced. He who has watched with apprehension the steady increase in frequency of the pulse in grave cases of pneumonia, typhoid, or the eruptive fevers, can scarcely suspect the signs of approaching

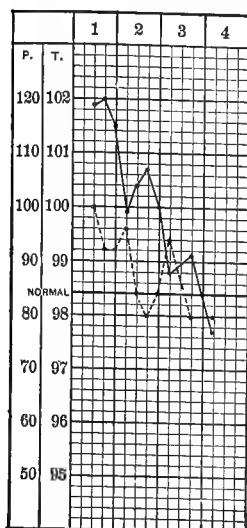


Fig. 5296.—Descending Type; Recovery.

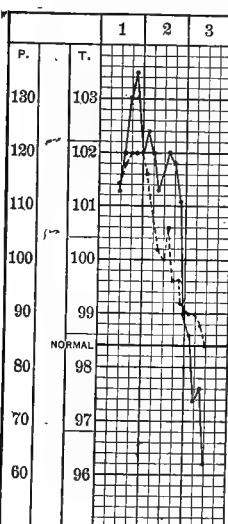


Fig. 5297.—Descending Type; Fatal on the Third Day. Suppression of urine, uræmia on the second day. Black vomit early the third day.

convulsions, the amount of urine being large and of low specific gravity. The patients are restless (see Fig. 5302).

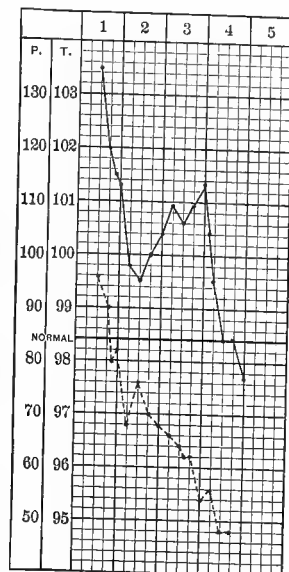


Fig. 5298.—Remitting Type; Recovery.

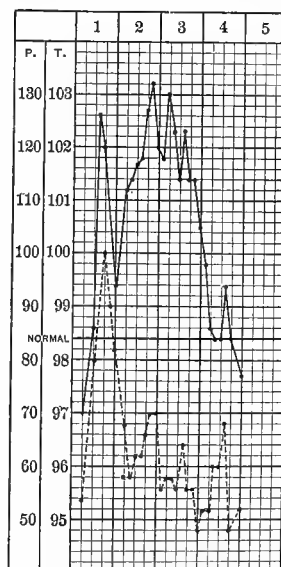


Fig. 5299.—Remitting Type; Recovery. Experimental case.

dissolution in a patient whose pulse is beating regularly and with fair volume at the rate of 70 per minute. There will be, however, a diminution of the blood pressure in such cases, with some coldness of the extremities, a cyanotic hue about the lips or of the whole surface of the body, and a sighing respiration, that should arouse our fears.

The slow pulse may show considerable tension, specially in cases in which the icterus is well marked. The frequent pulse of the last stages in fatal cases does not differ from the preagonic pulse we find in other diseases.

The Facies.—The face is decidedly flushed, suffused with red of the same hue as that of scarlet fever. The eyes are injected and bright. There is a slight tumefaction of the lids and the lips. Even on the first day we may notice already in connection with this injection of the superficial capillaries a fleeting shade of yellow. This early manifestation of jaundice is undoubtedly the most characteristic feature of the facies of yellow fever. There is really no distinct jaundice. In the

classical descriptions of the disease jaundice is not mentioned until the third day of the fever; but I hold that even at the earlier date we can detect a slight yellow tinge masked by the peripheral hyperæmia. Transient contractions of the capillaries will bring out this discoloration, for instance, in the imprints of the fingers when we pick up a fold of the skin, or in the conjunctivæ with the varying movements of the eyes. Often

more distinctly at a distance than upon close inspection we notice a faint yellow glimmer pass over the eye. The same is true of the face, as may be seen when the facial muscles contract in speaking or smiling, and the redness transiently pales. Later in the disease, about the third day, these waves of color may become quite decided. The redness begins now, specially in severe cases, to assume a purplish hue; the jaundice becomes more pronounced, and the contrast between the two colors is sharper.

The features above described are, of course, more striking in the fair Northern races. It is only in connection with the darker races that we

The mental attitude and the subjective symptoms have their natural influence upon the facial expression. During the first day the eyes are frequently closed on account of the photophobia, and the expression of the face is that of pain from the cephalalgia and rachialgia. Later on, there may be somnolence, from which, however, the patient is easily aroused; but more frequently the expression is bright and alert, whether the mind be clear or not.

The mind is always clear in mild cases, and frequently also in the graver and fatal cases even to the last day.

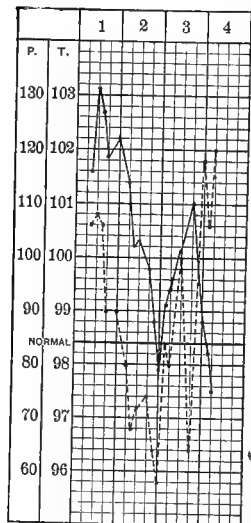


FIG. 5300.—Remitting Type; Fatal. Anuria, Jaundice.

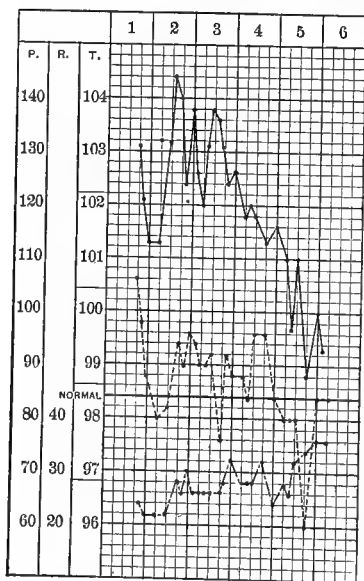


FIG. 5301.—Remitting, Irregular Type; Fatal. Albumin in the urine on the morning of second day. Gastric hemorrhage begins with the drop of the temperature on the evening of the second day, and continues abundantly to the end. Urine scanty, loaded with albumin. T., —; P.,; R., — — —.

may accept the descriptive simile made by those who liken the color of the skin in yellow fever to that of mahogany.

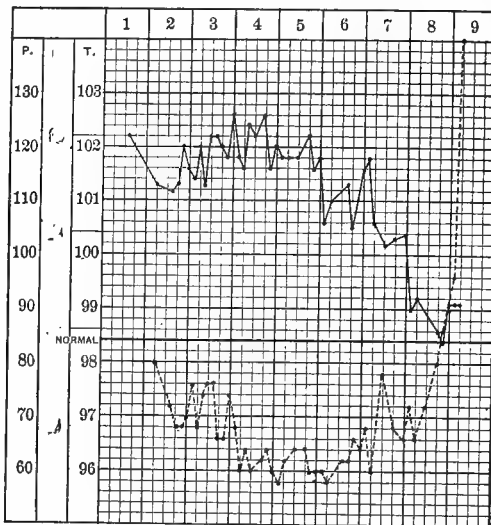


FIG. 5302.—Continued Type; Fatal. Black vomit begins at 7 P.M. on the seventh day, and is never profuse. Convulsions.

The excitement, the panic, that prevails in cities invaded by the epidemic, reflects upon the minds of the patients in the Southern States of the American Union. They are alert, watchful, suspicious as to the nature of their disease. They are apt to be nervous and excited. The Spaniard in Cuba who takes, or rather used to take, the disease as a matter of course is more calm or indifferent. All patients are apt to be rather talkative, and the dry mouth, the rather precipitate speech, reminiscent in character, are peculiar, and may be premonitory of a

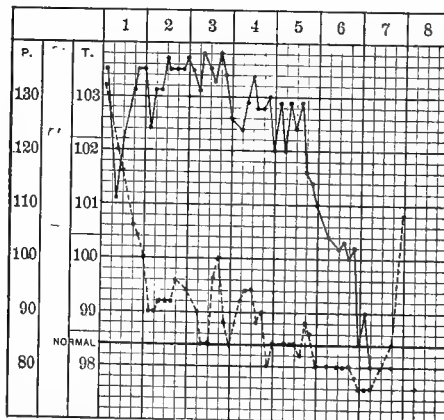


FIG. 5303.—Continued Type; Fatal. Black vomit once, at 2 P.M. of the sixth day. Delirium. Convulsions. Urine of the sixth day 1,180 c.c. with a specific gravity of 1.010. Albumin appears on the second day and is never abundant.

rather active delirium. If there be stupor it may be somnolent or wakeful, and accompanied with a staring expression. The delirium is talkative, and may be gay

or furious, generally dominated by some fixed idea; a notion that there is some urgent reason for the patient to leave his bed and quarters. His attempts to do so are, however, generally aimless, and limited to tossing about and sitting up in bed. It is very seldom that any restraint becomes necessary. Quite often there is, after the partial or complete loss of consciousness, a persistent and loud moaning which may be kept up during one or two days before death. Some cases of long duration present all the features of the typhoid state. Finally, we may have profound coma or convulsions.

Psychical disturbances, usually transient, may show themselves during the convalescence. I think they are less common than in typhoid fever and influenza.

Pains.—The supra- and intraorbital pains are perhaps the most distressing and persistent. They often disappear after the invasion, to recur with secondary elevations of the temperature or as a uræmic manifestation. The pains in the back and limbs may also be very distressing, and may even cause the patient to cry out in anguish. I have met with such severe aching only in cases of smallpox. In light attacks, however, the pains may cause little or no distress. Occasionally there are marked hyperæsthesia of the skin and deep-seated tenderness of the muscles. During convalescence it is not very rare to meet with painful neuritis, specially of the lower extremities. It usually affects one leg more than the other, and is accompanied with paræsthesia and very slight paresis. In my experience there has been only one case of serious peripheral palsy with atrophy, lasting several months and ending in recovery. Articular pains are rare. They are probably due to secondary infections, and may be accompanied with slight swelling of the joint.

The Skin.—After the first or second day the skin is apt to be moist, or at least the perspiration can be readily brought out by warm covering, or hot drinks, or other diaphoretics. Even during the first two or three days a slight moisture may alternate with a dry burning skin. When there is a marked remission it may be accompanied with a profuse perspiration, whether the defervescence be final or not; so that an active skin cannot be looked upon as a favorable sign or the indication of a critical discharge. A moist, clammy, cyanotic skin is frequently met with in grave cases after the third or fourth day of the disease.

Odor.—These perspiring patients are frequently malodorous, especially when, as is not rarely the case, a forced diaphoretic treatment is insisted upon; but I have never been able to detect in yellow fever an odor that may be called specific.

Rash; Eruptions.—The redness of the skin, previously described, is usually most marked about the face and neck, but it may be circumscribed in patches like an irregular scarlatina, an erythema, or the eruption of dengue. Rarely, faint irregular blotches may be seen, resembling the initial rash of variola. Occasionally we meet with sudamina, and very rarely with discrete pustular eruptions. An erythema and excoriations of the scrotum have been described by some authors, but I believe them to be exceptional and connected with chronic affections of the skin in these regions.

Gangrene is an extremely rare complication of the later stages, or of the period of convalescence, of yellow fever. I have seen once gangrene of one leg as the result of a secondary endocarditis. Other forms of localized gangrene about the scrotum or about the mouth are probably connected with neglect in the management of the disease.

Suppuration is, I believe, less frequently met with in yellow fever than in any other infectious disease. Abscess of the liver, suppuration of the parotids, deep-seated muscular abscesses are mentioned in the literature, but I have never encountered such complications. It is probable, therefore, that the secondary infections, evidences of which appear to exist in the clinical history, are not caused by pyogenic micro-organisms. I have suggested that the *Shiga bacillus*, a member of the

hemorrhagic group, may be responsible for the secondary infections.

Digestive Apparatus.—The lips may be red and slightly swollen. In the later stages of the disease they will be purplish in severe cases. Herpes labialis is not common. The gums, specially of the upper jaw, are usually somewhat swollen on the second or third day, and covered with a thin creamy coating which is apt to form a faint line upon the gum at some little distance from the neck of the tooth. Later on, the gums are almost always spongy, and inclined to bleed, either spontaneously or upon pressure.

The tongue presents no symptom of interest. It carries no special coating, and may be somewhat pointed and red about the edges. In hemorrhagic cases when the hæmophilic symptoms have shown themselves, the tongue is usually pointed, smooth, crimson, and moist; it may also present bleeding cracks upon the surface. At the same time the mucous membrane of the mouth and fauces will show a similar appearance.

Exceptionally the parotids are the seat of swelling in the initial stage of the disease. This is probably due to inflammatory œdema. The tumor is rather soft, and disappears before the end of the attack. I have never seen suppuration of these glands.

The Stomach.—Vomiting is by no means a constant symptom in yellow fever. As an initial symptom I believe it to be more common in variola and scarlatina. At this stage it is merely vomiting of portions of food still remaining in the stomach, and occurs but once, at the beginning of the attack. Persistent vomiting is a grave symptom; it may continue upon the initial manifestation, or, more frequently, it will begin on the second or third day. As a rule the vomiting will cease if the stomach be given absolute rest. The vomitus, if we exclude the initial emptying of the stomach, consists of a watery, somewhat opalescent material, containing variable quantities of mucus. Later in the course of the disease, if the vomiting should persist, it is apt to become hemorrhagic, as will be shown at first by the presence of minute brownish and black specks floating on the surface; then the specks increase in size and number, the liquid becomes darker, until we have the characteristic black vomit. In these severe cases, in the intervals—which may be long or short—between the acts of vomiting, the patient is usually tormented with constant nausea, or distress and burning at the epigastrium, or hiccup, and a sensation of rawness and burning along the œsophagus. Black vomit may be absent in severe and even fatal cases, but then the black fluid will almost certainly be found in the stomach at the autopsy.

Vomiting is frequently absent in mild cases unless provoked by medication; but epigastric tenderness upon pressure is rarely absent. We should note also epigastric pulsation as a frequent symptom.

The bowels are usually sluggish, but amenable to the action of cathartics. The stools are often normal; they are not clay-colored, but in hemorrhagic cases they are frequently dark, tarry, or bloody.

The Liver.—Jaundice.—The liver is not appreciably enlarged, but may be sensitive to pressure. The lesions that will be described in connection with this organ are, in part, sufficient to account for the jaundice on the generally accepted theory of a hepatogenous origin. The areas of swollen, necrotic, dislocated hepatic cells; the round-cell infiltration of the peribulbar zone could evidently, and no doubt they do, give rise to obstructions in the canalicular system; but the liver cells do not seem to be very active in the transformation of blood into bile pigment; they do not themselves become overcharged with pigment as is usually the case in obstructive jaundice. In yellow fever the liver seems to be comparatively less jaundiced than are other organs and tissues. The excess of hæmoglobin in the blood would lend support to the opinion that we have here to do with a form of polychromic icterus, but the liver cells are so generally disorganized that one cannot readily accept their ability to elaborate and transform the excess of blood pigment.

Here, more so than in connection with any other disease, it seems to me that the clinician should be loath to give up altogether argument in favor of a hæmatogenous jaundice, or at least in support of the view that something else than bilirubin may give rise to the yellow discoloration.

Jaundice is seldom, if ever, absent in yellow fever. It may be very slight, perhaps disputed, in some mild cases. Also in the rapidly fatal cases it may not show itself until after death. The dead body is always yellow in this disease.

When speaking of the facies I have mentioned a slight yellow discoloration among the initial symptoms of the disease. I believe it may be observed sometimes before the actual invasion. This symptom is first noticeable in the sclerotics. Now it is here also that the distinct jaundice of the third or fourth day of the disease first shows itself. It may be limited to this region, or more frequently it extends, growing in depth, and invading the regions that were most intensely flushed during the initial hyperæmia, until the whole body may become saffron-colored. Usually the jaundice is not so intense as it is in cases of obstructive icterus, or in Well's disease; the color does not tend to assume a greenish hue, but is rather modified by the concomitant, more or less dusky, red, or purplish hyperæmia. The jaundice increases during two, three, or four days, and then disappears rather rapidly, leaving usually no traces by the end of convalescence. The intensity of the jaundice is not of itself a symptom of grave import, especially if it be not accompanied by a marked hemorrhagic tendency; but the early manifestation of the symptom, a well-developed jaundice, for instance, on the second day, indicates a fatal termination.

The Urine.—Quantity and Specific Gravity.—The daily averages for cases of seven days' duration, all ending in recovery, are given in the following table:

Day.	Quantity. C.c.	Specific gravity.	Day.	Quantity. C.c.	Specific gravity.
First.....	820	1.020	Fourth.....	1,206	1.018
Second.....	991	1.017	Fifth.....	826	1.019
Third.....	1,084	1.018	Sixth.....	850	1.017

The daily averages for fatal cases of six or seven days' duration are represented in the following table:

Day.	Quantity. C.c.	Specific gravity.	Day.	Quantity. C.c.	Specific gravity.
First.....	775	1.022	Fourth.....	1,220	1.013
Second.....	809	1.018	Fifth.....	892	1.013
Third.....	1,113	1.015			

In the last two days the urine is frequently lost. The specific gravity is usually low, and the amount is reduced even to absolute anuria; though the cases are by no means rare in which the quantity and density of the urine are not seriously disturbed.

In all cases, mild or grave, the amounts of urea and of the chlorides gradually diminish during the fever.

Albumin.—The presence of albumin in the urine constitutes one of the chief characteristics of this disease. If we divide the cases of about one week's duration in two groups, those ending in recovery, and those ending fatally, we shall obtain the following instructive table:

Albumin appears	Recovered, per cent.	Fatal, per cent.
On the first day in	2	33
On the second day in	44	33
On the third day in	29	33
On the fourth day in	14	
On the fifth day in	8	
On the seventh day in	2	

In the large series of cases that constitute the basis of this article, albumin was found in all. It is true that some, that were perhaps cases of yellow fever, may have been excluded precisely because of the absence of this symptom; but, if accepted, they would have been at best but doubtful cases. In none of the infectious diseases is albuminuria so frequent a symptom. I must admit, however, that the careful examination made of the urine in all kinds of fevers has shown that this symptom is met with—more frequently than is generally believed—in influenza, typhoid, and malaria. In these diseases, however, unless the infection be severe, the amount of albumin is less, or the date of its appearance later, than in yellow fever.

Urobilin is frequently found in the urine, and bile pigments in the cases in which jaundice is a prominent symptom. An abundance of the latter is looked upon by some as a favorable sign. Azevedo and Couto report that they often obtain crystals of leucin.

Hæmaturia is rare, and hæmoglobinuria I have never met with in uncomplicated cases.

Albertini has shown, and I have confirmed, that the diazo reaction is not obtained in yellow fever. Its presence may be looked upon as very strong evidence against this disease.

Casts are found in all but the very mild cases of yellow fever. They may be hyaline, granular, or epithelial. Sometimes they are found in great numbers, and one cannot help being amazed at the rapidity of their disappearance, together with the albumin, during the convalescence, or even before the fever has entirely subsided. A chronic form of parenchymatous nephritis, following upon yellow fever, is to be counted among the rarest of sequelæ.

Retention of urine is not rare, but in my experience complete suppression is an uncommon and almost always a fatal complication.

Respiration.—The breathing is not accelerated except moderately during the last twenty-four hours in fatal cases. Frequent sighing and hiccough are rarely absent in the grave cases.

The Blood.—The maintenance of a high percentage of hæmoglobin during the first three or four days of the disease was first discovered by Finlay. Albertini has made a clinical application of this fact, and we have found in a large number of cases values ranging between 90 and 105. The specific gravity of the blood is not correspondingly high. It varies, in fact, between 1.040 and 1.060. In 32 cases of yellow fever examined with this point in view, the percentage of hæmoglobin has been found below 90 in 3; 70, 75, and 82 respectively. In other diseases, such as typhoid and especially malaria, the readings are almost invariably low. We consider this sign to be of distinct diagnostic value.

The number of red blood cells is not diminished. This fact, first observed by Finlay and Delgado, has been more recently confirmed by myself and by Azevedo and Couto. The increase in the number of erythrocytes and in the amount of hæmoglobin may persist until the fifth day of the disease. The red cells show no change morphologically or in their color reaction. The number of blood plaquettes is increased.

Leucocytes.—In yellow fever we have hypoleucocytosis without any characteristic variation from the normal relations of the several kinds of leucocytes. The hypoleucocytosis gradually disappears during convalescence, and is followed by some augmentation of the number. There may be hyperleucocytosis during the pregonic period.

The relative proportion of the different kinds of leucocytes I have found to vary as follows: Polymorphonuclear from 60.50 to 79.50 per cent.; lymphocytes from 14.10 to 36.40 per cent.; transition forms from 1.50 to 3 per cent.; large mononuclear from 1.78 to 9.50 per cent.

There is usually some increase of the mononuclears, but the readings are not so high as in malaria. The difference, as suggested by Gray, may be given some weight in the diagnosis, in the case of this disease. Eosinophiles are seldom found.

Hemorrhages.—Out of 277 carefully recorded cases, 123 presented hemorrhage as a noticeable symptom. Probably among the remaining 155 there were many with spongy gums that could be made to bleed slightly upon pressure. Of the non-hemorrhagic cases 148 patients recovered and 7 died; of the hemorrhagic 66 recovered and 56 died. The fatal cases had, with few exceptions, gastrorrhagia; most of them had at the same time other forms of hemorrhage. Of the patients that recovered 27 had black vomit. In most of these, however, the symptom was not pronounced; that is, the vomitus contained only more or less numerous specks of altered blood.

The character of the black vomit varies from the fluid just described, or one containing brownish flakes or striæ of a bright red color, to a black syrupy fluid. The amount varies considerably. Sometimes large quantities are repeatedly ejected with force to a considerable distance. In fifty-two per cent. of the cases the first manifestations of black vomit present themselves about the fourth and fifth days. I have seen it as early as the second and as late as the eleventh day. There can be no doubt as to the nature of the dark fluid under consideration. The microscopic, chemical, and spectroscopic investigations show the presence of variable quantities of altered blood.

Bleeding of the gums and nosebleed are the most common forms of hemorrhage in yellow fever. Black vomit follows in frequency; but we should not forget that it is not always an evidence of gastrorrhagia, since the blood may have been swallowed from the mouth or nasal cavities. Melæna frequently occurs as a result of the hemorrhages above described, or from enterorrhagia.

Bleeding from the uterus and rectum, petechiæ, cutaneous hemorrhages are all quite frequent. Minute hemorrhages and more or less extensive ecchymoses are found in the internal organs post mortem.

As an explanation of these hemorrhages I have suggested the possibility of secondary infections with bacteria of the hemorrhagic group. I have once had the opportunity of testing the blood serum of a hemorrhagic case with a culture of the Shiga bacillus, and I found a positive agglutination with dilutions of 1 to 50. It is well known that the blood of yellow-fever patients will agglutinate at times the Zanarelli bacillus, and that the latter may be found in the tissues.

The hemorrhages usually occur with a falling temperature, and it does not seem quite clear that the fall is a consequence of the loss of blood. I rather incline to the view that both phenomena have a common cause.

Complications.—If we exclude the accidents that may occur in the course of the disease, and that have been already described, we may say that complications are quite rare. Pulmonary and cardiac inflammations are very infrequent. The authors of the excellent monograph in Nothnagel's "Specielle Pathologie," Azevedo and Couto, believe that endocarditis is a common complication, but such has not been my experience, nor that of American and Cuban observers.

Malaria is not a very rare complication. Its symptoms usually remain in abeyance for three or four days, and then resume their periodic character. The complication is a serious one, but by no means necessarily fatal.

Relapses.—Relapses are very rare. Accidents may occur in the course of a slow defervescence, giving rise to renewed fever; but a second attack, interrupting the course of convalescence, I have seen but once in carefully observed cases. I also have the records of a second attack occurring six weeks after complete recovery from the first. Both attacks were severe.

Termination.—The return to health is usually rapid. In the second week the patient clamors for food, and is anxious to resume his avocations. In severe cases the favorable result may be delayed by prostration, anæmia, impaired digestion with or without jaundice, paresis of the extremities, neuritis. Death results, in the majority of cases, apparently from intoxication affecting the nerve centres and from hemorrhage. Ataxic symptoms, delirium, convulsions, coma, crowd one another in the last

hours of fatal cases of short duration. Other cases, usually with intense jaundice, have a less violent end, and die in an adynamic condition by asthenia.

DIAGNOSIS.—The diagnosis rests mainly upon the four chief symptoms: the facies, the pulse and temperature, the albuminuria, and the tendency to hemorrhages.

In certain diseases, usually benign, such as influenza and dengue, that may be confounded with mild cases of yellow fever, the diagnosis is at times difficult. At the beginning of an epidemic the examination of several patients may be necessary.

In influenza we should expect to find the catarrhal symptoms, the peculiar appearance of the buccal mucous membrane and the tongue, the greater remissions of the fever, the pulmonary complications, the presence of the influenza bacillus. In yellow fever, on the other hand, we should find jaundice and albuminuria much more frequently than in influenza of the mild type that we are here concerned with; and then, besides, in yellow fever there is the peculiar pulse line.

In dengue we would rely upon the eruption and the articular and muscular pains, and upon the absence of jaundice and albuminuria.

With respect to graver forms of yellow fever it may be difficult to determine whether we are dealing with this disease or with typhoid, malaria, and malignant forms of jaundice, or, more rarely, with plague and relapsing fever.

Typhoid Fever.—Each one of the two diseases—yellow fever and typhoid fever—has its special facies. During the first week, when the mistake is likely to be made, the tongue in typhoid is heavily coated. The temperature is more regular, and the pulse frequency does not decrease. I need not mention other symptoms generally found in typhoid; but our opinion will be guided by the following facts: In typhoid our patient has probably been sick with fever two or three days; he is likely to have a temperature of 103° F. or thereabout. The following day he will have the same temperature. Now in yellow fever this would mean a quite severe form of the disease, and the patient ought to have a well-marked albuminuria. In typhoid he will have but little or no albumin. This may appear as a matter of little importance, a mere difference in degree, but it is not so. The pronounced albuminuria of severe cases of yellow fever is a very striking symptom, quite distinct from mere febrile albuminuria. The albumin may increase in typhoid, but a case of yellow fever with the temperature of a typhoid patient, kept up for several days, would be in a very grave state, and would show all the alarming and peculiar symptoms of the former disease. Besides, in typhoid we should have the diazo reaction in the urine, and a low percentage of hæmoglobin in the blood. At the time when the Widal reaction is obtainable the case is not likely to be mistaken for one of yellow fever.

Malaria.—The plasmodium in the blood in malaria, and the albuminuria of yellow fever are the main distinctive features. A great deal has been written about a certain form of malaria as likely to be confounded with yellow fever; I refer to the bilious remittent fever. I suspect that this name was generally given to the yellow fever of the natives of the yellow-fever zone who were supposed to enjoy immunity against this disease, or else it is a form of malaria that has disappeared from our malarial regions.

The real difficulty in diagnosis is encountered in connection with cases of æstivo-autumnal fever during the first days of the attack, and with cases of yellow fever in the first stage of the disease. It is precisely the absence of the so-called bilious symptoms at this time in the latter disease that renders the diagnosis difficult. We may have to wait for their appearance, as they are sure to come in a case of yellow fever having the high temperature and the stormy onset of the tropical form of malaria in an unacclimated person. The same may be said of the albuminuria; it will be a striking symptom of such a case, whereas in malaria, if present at all, it will be no more than an ordinary febrile manifestation. In

this disease the tongue will be flat, flabby, and coated; the liver and spleen will be enlarged; the hæmoglobin percentage will be about seventy or lower; the temperature is likely at some time to fall precipitously without any hemorrhagic symptoms; the pulse is sure to rise with the following access of fever; the malarial parasites will be found in the blood. We should remember also that a yellow-fever patient with the high temperatures that are likely to prevail in malaria, is a very sick man, whereas the malarial patient is less seriously affected.

In hæmoglobinuric fever the black water itself is very strong evidence against yellow fever, especially if we can prove the absence of red blood cells in the urine. The attack usually comes on after repeated paroxysms of intermittent fever with a severe chill, and the hæmoglobinuria and the jaundice, the enlargement and tenderness of the liver and spleen, with anæmia and low per centages of hæmoglobin in the blood, are prominent features from the start.

Malignant Jaundice.—Writers who were not familiar with yellow fever have supposed that there must be a marked resemblance between these affections, but this is not true. In acute yellow atrophy we have the following distinctive features: frequency of the disease in connection with pregnancy, prodromal gastro-hepatic disturbances, early development, and progressive character of the jaundice, absence of the sudden onset with fever and congestive symptoms, diminution in the size of the liver, change in the color of the faeces, presence of leucin and tyrosin in the urine, marked diminution of the amount of urea, great prostration, pallor, low percentage of hæmoglobin, and slight oedema.

In Weil's disease the history of the onset corresponds with that of yellow fever, but the gastro-hepatic symptoms are more pronounced from the beginning. The jaundice is more intense and presents a more greenish tint. There is a tendency to diarrhœa; the faeces are often clay-colored. The liver and spleen are large and tender. The muscular masses are sensitive to pressure. The hemorrhages, when present, are a later manifestation than in yellow fever. The duration of the disease is longer, its course being frequently marked by two distinct paroxysms. The patient falls very soon into a typhoid state, and finally the urine, according to some authorities, is apt to contain the *Proteus flavescens*.

Prognosis.—Attention has already been given to the prognostic significance of the several symptoms; hence it is not necessary to dwell extensively upon this subject. We may summarize the unfavorable prognostic signs as follows: maintenance of the temperature at a high level for several days; high temperatures coinciding with the appearance of the jaundice and hemorrhages; persistent vomiting after the initial emptying of the stomach; noticeable falls of the temperature after vomiting, with subsequent elevation; marked reduction of the arterial blood pressure; early development of pronounced jaundice, albuminuria, or gastric hemorrhage; loss of consciousness with active delirium or with a staring expression; profound coma; suppression of urine.

The mortality from yellow fever varies in the different epidemics. The series of 277 cases treated at Las Animas Hospital in Havana, which have been specially analyzed in this paper, gave a mortality of 22.7 per cent.

I have myself seen the range of mortality vary, in different epidemics, between 4 and 36 per cent. Among soldiers confined in barracks the mortality is said to have been as high as 92 per cent. It is low among children and very low in the full-blooded negro. I have not been able to find any decided differences in the mortality of the whites from the various nations. Reports to the contrary are, in my opinion, to be explained by accidental conditions affecting at the time one race more than another. The natives of one country, for instance, will be better looked after; they will come in for treatment earlier than others. At Las Animas Hospital the mortality among those who were admitted within the first forty-eight hours of the disease was 17.7 per cent., while among those who were admitted later it rose to 32.3 per

cent. Now, the first were mostly Americans; the second were Spaniards, Italians, etc.

Before concluding this description of yellow fever I wish to state that though I have made special use of the material at my disposal, which is derived from the study of cases in Havana during 1900 and 1901, my knowledge of the disease is based upon the study of many epidemics observed in the United States, in Cuba, and in Mexico. I mention this because I wish to declare that I have found the disease everywhere and at all times to be always the same. The number of mild cases will be greater at one time than at others. There may be a difference in intensity; but, aside from this, I have never been able to discover characteristic features that would distinguish one epidemic from another.

MORBID ANATOMY.—External appearance of the body. The cadaver of yellow-fever patients presents a characteristic coloration. The shade of yellow is variable up to a deep saffron color. This is not uniformly distributed as in other forms of jaundice, but rather appears with greater intensity in the depending portions of the body. At the same time we find extensive areas of cadaveric lividity due to hypostasis. The face appears livid and turgid. From the mouth and nostrils we generally find oozing a dark fluid, or dark crusts or coagula are found about these orifices. The conjunctivæ are yellow and often ecchymotic.

The Heart.—This organ is not as a rule seriously affected in yellow fever. This opinion does not conform with that of Soudré and Couto as expressed in Nothnagel's "System of Medicine." The size and weight of the organ are normal. The consistence is generally firm, with few exceptions. The external aspect indicates in some cases a slight increase of the subpericardial fat, specially toward the base, and along the transverse and longitudinal furrows. This is not an evidence of degeneration since the underlying muscular tissue is generally found to be normal. On the surface we may find a few ecchymotic spots, but they are not more numerous than those found elsewhere. Soudré and Couto describe in one case a hemorrhagic focus about the size of an almond, involving the whole thickness of the left ventricular wall. On opening the heart the muscle appears somewhat paler than normal, and the thickness of the ventricular wall is normal, or may be slightly increased. This is described as constant by Couto and Soudré. The left auricle and the right side present nothing abnormal. Some post-mortem clots are generally found in the cavities. The endocardium presents to the naked eye, in some cases, a yellowish discoloration, more marked toward the tendinous extremities of the papillary muscles. Ecchymotic points may be seen generally near the large vessels. These are not constant changes. The valves may be slightly thickened toward the borders, but usually they are normal. The valvular thickening and vegetative endocardial lesions described by Couto and Soudré as constant, we have not been able to find.

Histology.—Alterations of the muscular fibre occur only in rare cases. The striation, which is never as distinct in the cardiac as in the voluntary muscles, shows quite clearly in most of our preparations as soon as we apply the sufficient amplification. The continuity of the fibre is not altered, and it is well known that in the degenerated heart this is easily broken. The nuclei take the stains readily, and do not present the deformities and elongations that are found in other infections. The interstitial connective tissue is not increased or proliferated. The vessels show no alterations. Occasionally we find small extravasations near the endo- or pericardium. The subpericardial fat appears to be somewhat increased. This probably explains the augmentation in the size of the organ. Rarely we have met with alterations in the muscular fibre. These are by no means uniform. More or less granular cells are found among perfectly normal ones. The former are slightly vacuolated, and their stri-

* This section has been written by Drs. Juan Guiteras and A. A. Aballi.—EDITOR.

ations may be completely lost. The nuclei will be found to take the stains, and to show no profound alterations. The fatty degeneration, described by others, we find to be exceptional. Nowhere have we found evidences of acute endocarditis. In one case we found a minute accumulation of round cells, separating muscular fibres which were perfectly normal.

The pleura and lungs present no lesions that are characteristic of yellow fever.

The Spleen.—Its size is usually not altered. On section the pulp presents a dark wine color, with reddish areas. The Malpighian corpuscles are not prominent. The consistency of the organ is somewhat diminished. Histologically we find the organ but slightly affected. The Malpighian bodies show neither proliferative nor degenerative lesions, but the connective-tissue stroma appears to be slightly increased. The parenchyma of the organ is congested. The small veins are particularly distended. In some cases we met with hemorrhagic foci. There is no increase in the amount of pigment contained in the spleen. Some authors describe cloudy swelling limited to small areas of the parenchyma. This we have not been able to confirm, nor have we found any appreciable change in the vascular walls.

The Kidneys.—By the naked eye we discover profound lesions that appear to be constant. The size is more or less increased. The color is generally yellowish-red. Upon section the color appears reddish-yellow or grayish. The vessels are dilated and the blood flows freely. The medullary zone contrasts with the cortical through the normal or somewhat cyanotic hue of the former. The capsule peels easily, and the surface appears reddish-yellow with vascular arborizations.

Morbid Histology.—Two kinds of lesions are found in our preparations: one is constant and the other variable. The glomeruli, though sometimes normal, present in most instances evident lesions. At times the capsule is thickened through proliferation of its cells, but it is more frequently normal, except that the epithelium, parietal or visceral, is more or less degenerated. The cavity is generally filled with an exudate of variable character. It may be granular, containing exfoliated cells, or it may present minute fatty areas or evidences of hyaline degeneration. The exudate takes a rose color with the hæmatoxylin-eosin stain, or gives the reactions of hyaline matter. The capsular degeneration does not appear to be constant; nor is it necessarily fatty, even in cases in which the fatty change is quite apparent in other portions of the kidney. The glomerule is retracted and small in proportion to the amount of exudate, and it rarely shows evidences of cloudy swelling. In our experience the more constant lesions are found in the convoluted tubules. Their lumen may be dilated, and contains granular matter from the disintegration of cells and from the coagulation of albumin. Together with this material we find cells in a more or less degenerated state, and fragments of the same, in conjunction with deformed free nuclei, still capable of taking the basic stains. In some places we find hyaline masses, true casts, filling the lumen. In preparations stained after Marchi, Golgi, or Weigert we find here and there fine fatty granules or droplets of varying size. This is by no means always the case, for we find many tubules in an advanced state of degeneration without signs of the fatty reactions. We have not been able to find the colloid bodies and crystals described by Councilman. The epithelial lining of the convoluted tubules is intensely degenerated, in the shape of cloudy swelling or fatty change. Osmic-acid preparations, stained by safranin and carmine, will show cells infiltrated with fat, and still presenting complete integrity of the nucleus. Mitotic figures are rare. We find also the special form of necrosis described by Councilman, namely, minute, rounded, or irregular bodies, well differentiated from the protoplasm. They stain intensely with eosin, and should be studied with high powers. The straight collecting tubes, the descending loop of Henle, the excretory ducts are less affected. Here the integrity of the epithelium is

better preserved, and the form of degeneration most frequently encountered is the cloudy swelling. The tubes in the pyramids are often obstructed with cylinders corresponding with those that are found in the urine. The interstitial connective tissue also participates in the process. We find recent round-cell infiltrations around the glomerules (periglomerulitis), and about the cortical and medullary tubules. In some sections the infiltration is such as to invade the tubules themselves. The epithelial cells are found degenerated and compressed among connective-tissue cells of new formation and leucocytes.

Twice we have met with small abscesses of the kidney at the line of contact of cortical and medullary portions. Bearing upon the question of secondary infections we should state that one of these cases was of short duration.

The renal vessels are at times dilated, especially the larger ones, the interlobular and arciform; but no appreciable changes are found in the walls of these or of the smallest vessels. Hemorrhages are rarely met with.

We may classify the renal process in yellow fever as a hæmatogenous acute parenchymatous nephritis.

The Stomach.—The size of the organ is normal or slightly increased. On opening the viscus we find always more or less of a dark fluid, resembling coffee infusions of variable density. Frequently we find remnants of food, and at times fine shreds of mucous membrane. The spectroscopic, chemical, and microscopic investigations show that the coloring matter of this fluid is hæmoglobin or some one of its derivatives. The mucous membrane presents a reddish-gray color and ecchymotic points especially about the cardia and pylorus. The remainder of the surface presents also reddish points corresponding with the dilated vessels.

Histology.—The changes found vary in different cases. Sometimes they are limited, in the mucosa, to a simple congestion, specially characterized by a distention of the intertubular vessels that empty into the veins of the submucosa. In these cases only the superficial part of the mucosa is altered. The nucleus and the protoplasm do not take the stain well, but the epithelium is generally preserved. Such losses of it as may be encountered are to be ascribed to cadaveric changes. We find in these stomachs small superficial hemorrhagic foci, and at times small extravasations, but without any evidence that the capillaries have suffered in their integrity. Over the places just described the more superficial layers of the epithelium are degenerated, and the cells are found mixed in a magma composed of exfoliated cells, altered red globules, and free pigment. Other cases present deeper lesions. These are more pronounced toward the fundus and pylorus, especially the former. The chief or central cells of the glands present lesions that are characterized by lack of affinity with the hæmatoxylin, and a granular condition of the protoplasm; but we have not been able to demonstrate the presence of fat. These alterations do not generally affect uniformly the whole length of the gland. In the glandulæ propriæ of Kölliker we find normal chief cells alongside others more or less degenerated. The fundus of the gland is generally less affected than the periphery. In these cases the interstitial connective tissue participates in the degenerative process. This tissue presents a certain degree of translucency, and a lack of definition of its elements. These alterations are more manifest in the superficial layers. These do not stain distinctly with the eosin or with the fuchsin in van Gieson's process. The elastic fibres cannot be easily distinguished. We have seen no evidence of active connective-tissue proliferation, such as is found in most of the forms of gastritis, specially the hemorrhagic. We do find accumulations of round cells in the mucosa and submucosa, but without evidences of degeneration or active proliferation. The submucosa presents small areas of degeneration in the muscularis mucosæ. We have not been able to discover the punctated appearance described by Couto and Soudré. The vessels are often dilated, but no alterations can be found in their walls. The lumen is generally packed with red cells and a few leucocytes. In one case connective-tissue

elements of new formation were found infiltrating the sub-mucosa about the veins, but even here no change could be demonstrated in the vascular wall. The muscular coat is normal in volume and shows no signs of degeneration. Distended vessels are seen among the layers of the musculature. The fat of the subserosa is not increased, nor is this membrane in any way altered.

The Intestines.—The lesions vary with the form and intensity of the infection. In those cases in which there have been intestinal hemorrhages the lesions are more intense. Invaginations of the small intestines have been met with. In one of our cases there were two such dislocations: one, at 1.5 metre from the duodenum, and the other 30 cm. lower down. There were no adhesions nor inflammatory exudate upon the serosa, but simply a congestion of the invaginated portion of the intestine.

On opening the intestine we find the color to be normal, except at some places where a reddish and cyanotic discoloration is apparent. This is more marked in the upper part of the intestine. Peyer's patches are not swollen or ulcerated. Histologically we find no serious lesions of the mucosa. It is less congested than that of the stomach. In most of our preparations there are marked cadaveric lesions, specially toward the duodenum. The epithelium covering the villi may be wanting or macerated, but it is generally present. The glands of Lieberkühn show no evidences of catarrhal inflammation, and the cells of the glands of Brunner present nothing abnormal. We find no abnormal round-cell or leucocytic infiltration. In hemorrhagic cases we find foci similar to those described in the stomach. The sub-mucosa and the serosa are normal.

The large intestines are usually not affected. When we meet with lesions they are generally encountered in the lower portions of the gut and are catarrhal in character. The rectum generally contains fecal matter, the consistence of which varies considerably. Hemorrhagic lesions are occasionally met with.

The Liver.—The volume of the organ is normal or slightly augmented. In 60 autopsies performed by Couto and Soudré the weight averaged 1,680 gm. The minimum was 1,200 and the maximum 2,200 gm. In 8 cases it varied between 1,400 and 1,500. Thirteen cases, investigated by Dr. Araujo Vianna, gave a specific weight as follows:

Absolute weight.	Specific weight.	Weight of the fat extracted by ether.	Absolute weight.	Specific weight.	Weight of the fat extracted by ether.
1900	1.045	226	1575	1.054	283
1610	1.037	236	1200	1.048	192
1500	1.079	185	1650	1.058	203
1750	1.071	233	1760	1.037	369
1915	1.052	204	1400	1.083	56
1770	1.022	306	1450	1.085	43
1800	1.028	420			

Color.—The color of the organ is characteristic of the disease. It may be compared with new leather or box-wood. Minute reddish points are generally found on the inferior surface. On section we observe the same discoloration, and we notice some reddish-gray points corresponding to portal spaces. The gall bladder usually contains small quantities of bile of dark color and syrupy consistence. The biliary passages are patulous, and on compression of the gall bladder the bile flows freely into the duodenum.

Histology.—From the study of our cases we conclude that the liver is the organ most seriously affected in yellow fever. We are at once struck by the deformity and disorder that prevail in the hepatic lobule. The cells are not radially distributed around the central vein, and the vascular net appears more tortuous than normally. Foreign elements, such as leucocytes and connective tissue of new formation, among the hepatic cells, give rise to this disorder. The protoplasm of the cells is more granular than normally, and presents vacuoles of vary-

ing size. These gradually gain upon the protoplasm until they invade it totally. Highly refractive hyaline bodies, more or less rounded generally, but at times presenting slight prolongations, are found in the cells and between them. These bodies take the eosin stain intensely, and take an orange color by the van Gieson method. According to Councilman they represent a partial necrosis that is characteristic of the acute fatty degenerations of the liver. ("Report of the Etiology and Prevention of Yellow Fever," by George M. Sternberg. "Report of the United States Marine Hospital Service," 1890.) The nucleus, usually excentric, generally stains well with the basic colors. This integrity of the nucleus contrasts in a remarkable manner with the disintegration of the protoplasm, and probably explains the rapid recuperation of the functional activity. Some nuclei are degenerated, as evidenced by signs of caryorrhexis and vacuolization. This occurs especially in the neighborhood of the portal spaces. Here also we meet occasionally with evidences of proliferation: double nuclei, various manifestations of mitosis, and small hepatic cells. In preparations colored by the Marchi method, or fixed in Flemming's fluid, we find that the vacuolizations of the protoplasm represent simply fat globules. These take the black color with the osmic acid. Their number varies from two to four, or they may run together, occupying the whole body of the cell. We rarely find necrotic areas. In one case the necrotic areas were confined to the periphery of the lobule, while the central portion, charged with fat, presented a normal coloration of the nuclei.

The interstitial connective tissue participates actively in the pathologic process. This is especially true in the portal spaces, where we encounter accumulations of round cells gathered around the blood-vessels and bile-ducts, and frequently pressing upon the latter and obliterating their lumen. This obliteration is not constant, for we meet with open ducts even in the midst of the proliferated connective tissue. In the interior of the acini we find also a considerable number of round and fusiform cells, together with fibrillæ of connective tissue and a few leucocytes.

It is a remarkable fact that we meet nowhere with evidences of a decided pigmentation of the organ. The free pigment is relatively scarce. It is manifested by a finely punctuated appearance, and does not give the iron reactions. Pigment is also found within the cells. The scantiness of pigment in the yellow-fever liver is in strong contrast with the findings in other forms of jaundice. The walls of the biliary passages are normal.

The blood-vessels of the liver present no alteration of the walls. Their lumen is not distended, and in their contents we find but rarely an increase of the leucocytes. Hemorrhages are very rare.

The Pancreas.—In the few cases in which we have studied this gland we have found only cadaveric changes. We could not demonstrate the existence of the fatty degeneration described by some observers.

The Nervous System.—The meninges are generally in a normal condition. Sometimes ecchymotic spots are found in the dura. The sinuses are generally found filled with blood in those individuals who die in a comatose state. The arachnoid, the pia, and the choroid plexus are congested, and occasionally we meet with small extravasations. On section the blood flows somewhat freely from the vessels. The ventricles are dilated. Their walls, as well as the cerebro-spinal fluid, are slightly stained yellow. The brain is of normal consistence, but somewhat softened in prolonged cases. On section the color is normal and the punctuated appearance is rather prominent. The spinal cord presents similar appearances with less prominence of congestive signs. The histology of the nervous system has not been carefully investigated.

TREATMENT.—The mortality statistics, referred to under the head of Prognosis (and they correspond with others from various sources) show the importance of early treatment in yellow fever. Not that we possess any specific that should be applied during the first hours of the disease, but that those patients are more likely to recover

who are put to bed at once, and who are kept on an absolute diet. Nothing else, if we except the administration of a laxative and the employment of some palliative measures, was done for the patients admitted to Las Animas and the Mercedes hospitals during the first two days of the disease. The results compare very favorably with those obtained without the proper sick-room discipline, and with active medication. I recommend in this connection the reading of a paper entitled "Notes on the Treatment of Yellow Fever at Las Animas Hospital," by Col. W. C. Gorgas, in the *Journal of the Association of Military Surgeons*, for October, 1903.

The patient should be put to bed at once and kept in the horizontal position. Clean linen for the bed and person should be furnished plentifully. Windows and doors should be left open (screened against mosquitoes, of course), care being taken to avoid only the direct action of strong currents of air. The quarters should be as clean as possible. Patients seem to do well when treated in tents, whereas the mortality is generally high in old yellow-fever hospitals. The skin should be cleansed and rubbed with hot water and soap, and clean, loose garments should be substituted for the clothing worn by the patient. It is not unreasonable to believe that these measures may lessen the chances of secondary infections. At any rate, the patients so treated do better than others.

A mild purgative—calomel and jalap or castor oil—is ordered, and water is given freely through a drinking tube or feeding cup. From fifty to eighty ounces of fluid are given in the twenty-four hours. Plain water, pleasant alkaline waters, ginger ale, lemonade, orange leaf tea, are given, preferably cold, though some patients call for warm drinks. Weak solutions of bicarbonate of sodium may take the place of mineral waters. The patient is not allowed to sit up to empty the bladder and rectum.

Absolutely no drugs are given until we see clear indications for them, a condition that is not likely to arise in a large number of cases, or only from the third day onward in the grave cases. During this interval much can be done to relieve the sufferings of the patient and to gain his confidence.

External applications should be freely used: light sinapisms to the back of the neck, to the calves of the legs, to the loins, or to the epigastrium; ice caps to the head or to the back of the neck; rubbing of the legs or back with alcohol or some liniment; warm applications over the bladder if there be retention of urine; sedative water to the forehead. If the body-temperature be very high the surface should be sponged with cool water and alcohol, or an enema of cold water may be given.

If by night time the patient be suffering much from pains in the back and head, a dose of five grains of phenacetin may be given, and repeated, if necessary, once during the night. After the third night this drug is scarcely called for, and its use is probably harmful.

The first symptom that is likely to call for special treatment is vomiting. If the bowels have not acted since the initial purge we should now give a Seidlitz powder in broken doses, or effervescent magnesia, or calomel in minute, often repeated doses. If the vomiting does not stop readily, we should discontinue the administration of liquids by the mouth, and allow nothing but cracked ice in small quantities. At the same time rectal injections of warm physiologic salt solution in doses of six ounces every four hours should be prescribed. It is to be hoped now that the rectum has not been made irritable by the excessive use of purgatives, for much depends upon the continued administration of these injections perhaps for several days. When we have reached the fifth or sixth day of the disease, the question of feeding these patients presents itself. If there has been no vomiting one ounce of milk may be given every two hours by the mouth; but if we have been forced to use the rectal injections, two or three ounces of milk should be injected with the salt solution.

If the vomiting and retching be very frequent, a few doses of cocaine in tablet form should be tried, or ice

may be applied to the throat. The oft-repeated vomiting is almost sure to lead to hemorrhage. Immediately upon the first appearance of brown flakes in the vomitus I prescribe tincture of the chloride of iron in five-drop doses every two hours. I give it usually with a little glycerin and lemon juice. The iron almost always reduces the frequency of the vomiting. I have tried adrenal extracts without success. If there be much hemorrhage from the mouth I prefer to use a mouth wash containing antipyrin. Wherever the source of the hemorrhage may be, I think the iron should be insisted upon.

The remainder of the treatment reduces itself to sustaining the strength of the patient, and stimulating the action of the heart and kidneys by the judicious use of strychnine and digitalis and alcohol; the two former by the hypodermic method, and the latter by the mouth or rectum. Alcohol is not well borne in large doses; a tablespoonful of champagne or some whiskey in carbonic-acid water, given occasionally when symptoms of collapse appear, is without doubt useful. Hypodermics of strychnine, or of digitalin in doses of gr. $\frac{1}{60}$ or gr. $\frac{1}{120}$ may be given every six hours with advantage. I do not believe these patients will stand as much strychnine as those suffering from other infectious diseases.

Digitalis is more specially indicated when the kidneys are inactive. In suppression of urine cold-water rectal injections have been recommended, and in some few cases I think I have done good through the diuretic action of calomel.

The prolonged typhoid cases, generally marked by intense jaundice, require alcohol and strychnine. Most of them have to take iron for a few days on account of the hemorrhages; but, as these subside, I think they are benefited by the use of small doses of chlorate of potassium. Later on, in the period of convalescence, they should take muriatic acid and nuxvomica.

As already mentioned, about the fifth day we should begin to give milk, with lime water, if necessary. The dose should be gradually increased, and about the ninth day a mild solid diet may be ordered. Ice cream is much relished, and may be given before this.

The patient should be allowed to get on his feet gradually, and in the majority of cases he is up and about at the end of the second week. Very mild cases will have recovered completely in ten days, while others will require the use of peptonized food, tonics, and massage for a few days.

PROPHYLAXIS.—The perfect success of the prophylactic measures against yellow fever is based on the complete knowledge we now possess of the mode of propagation of the disease. It is transmitted by the *Stegomyia fasciata*; the insect becomes infected by biting the yellow-fever patient at any time during the first three days of the disease; the insect becomes infecting twelve days after it has bitten the yellow-fever patient. The application of this knowledge to prophylactic practice is perfectly feasible.

The patient should be treated, if possible, within an enclosure known to be free from the *Stegomyia* mosquito. In cities exposed to the introduction of yellow fever there should be kept always in readiness such an enclosure—a mosquito-proof ward. In the city of Havana we have no hesitation in receiving cases of yellow fever from the shipping. We have, almost forcibly and with the idea of protecting the ship and the port to which it was bound, removed such a patient from a vessel and brought him into the city. Our security in this city depends simply on our having such an enclosure. The patient is brought under a mosquito bar to the mosquito-proof wards of Las Animas Hospital, where he is cared for by attendants, many of whom are non-immunes. This has been done now for three consecutive summers without a single instance of propagation of the disease.

If the patient must be treated at home steps should be taken to screen the windows and doors. If possible a room should be first fumigated to destroy the mosquitoes, and screened before the patient is brought into the apartment.

It is apparent that the source of infection, the patient, is quite under our control in most instances. Of course the possibility always exists of mild ambulatory cases that may escape our observation. I have always thought that such cases, specially among the negroes, are responsible for the spread of some epidemics.

If the patient has had the opportunity to infect mosquitoes before he comes under observation, it becomes necessary to destroy the infected insects. Here, again, we observe how completely this disease is under our control. The insects give us time to act. They can do no harm before the lapse of twelve days. Furthermore the *Stegomyia* mosquito is a domestic insect. It is not likely to migrate far from the patient. It will remain in the same room or at least in the same house. If the patient's quarters are protected against the smoke, the other parts of the building may be fumigated with pyrethrum. The houses immediately adjoining should be fumigated at the same time. After the recovery or death of the patient the room occupied by him should also be fumigated.

Although the pyrethrum is not so certain an insecticide as are certain other substances, it is more manageable, and can be applied in all places and at all times. If care be taken, during fumigation, to leave a sheet of paper, wet with mucilage, under a glass window, or under some opening pasted over with paper, the insects are sure to fly to the light, and will drop, when paralyzed, upon the paper beneath. In this manner, and by carefully sweeping the room, before freely opening the windows, after fumigating for four hours, we are quite sure of collecting all the mosquitoes. These should be burnt at once, or placed in a bottle, if we desire to determine the kind of insects found in the premises.

The complete success attained in Havana by these methods was in part due to the fact that most of the patients affected with yellow fever were hospital patients; that is, they could be removed at once to Las Animas, or to some of the private hospitals in which the sanitary department had seen to the preparation of adequate wards.

A fine was imposed on the physician who failed to report a case of yellow fever, and a commission of experts, whose opinion as to the diagnosis was final, visited the patient at once, and reported upon the nature of the disease. Preventive measures already instituted were continued or not according to the finding of the commission.

At the same time that these direct measures of prophylaxis are being carried out, every effort should be made to diminish the number of the *Stegomyia* mosquitoes in the locality. Deposits of water of all kinds should be reduced to a minimum. Waste waters, sinks, and pools should be frequently oiled with petroleum, and water barrels, tanks, and cisterns should be screened.

The above simple method of prophylaxis is based on the well-known studies of Dr. Finlay, and Drs. Reed, Carroll, Lazear, and Agramonte. These authors had left undetermined the duration of the period of infectivity of cases of yellow fever. From their experience and my own it appeared probable that this period of infectivity was limited to the first three days of the disease. In the report of the French commission (Marchoux, Salimbeni, Simond) sent to Rio by the Pasteur Institute, we find (*Annales de l'Institut Pasteur*, November, 1903) that special attention was paid to this point, and that inoculation experiments were made to show that a case of yellow fever on the fourth day was not capable of transmitting the disease.

The experimenters of the French commission have immunized individuals by injecting serum of yellow-fever patients previously treated by heating for five minutes at a temperature of 55° C., or by keeping it under a layer of vaseline during eight days. Dr. Carroll had already suggested the attenuation of the virus by heat. The commission also show that the serum of convalescents possesses preventive properties, and perhaps curative properties, as suggested by Finlay.

Juan Guiteras.

YELLOW VISION AND OTHER FORMS OF CHROMATOPSIA.—Chromatopsia is a modification of the visual sensation, as a result of which all objects appear of a certain color (red, purple, blue, yellow, green, white), without any effect upon the acuteness of vision or any visible changes in the fundus.

Erythropsia (*Red Vision*), the most common variety, is not infrequent after cataract extraction, occurring in three to five per cent. of cases (Becker), and after exposure to intense light, for example, sunlit snow fields especially in high regions, brilliant electric light, flashes of lightning, and observation of the sun. This visual disturbance becomes more marked when the illumination is suddenly diminished, as after going from the open into a house. After cataract extraction there is less frequently purple or blue vision (*kyanopsia*), or the patient complains of objects appearing of a glaring white. The phenomenon generally appears shortly after the operation, or after some days or weeks; it lasts a variable number of hours, days, weeks, or months; it may be constant or intermittent; it generally disappears in the course of a few days or weeks. No treatment is called for beyond the wearing of smoke-tinted glasses; potassic bromide has been recommended in these cases.

Independently of cataract extraction, the occurrence of colored vision is favored by dilatation of the pupil, congenital coloboma of the iris, iridectomy, by excitement of any sort, and by elevation of body-temperature. Red vision is an occasional symptom of optic-nerve atrophy, glaucoma, nyctalopia, migraine, hysteria, hysterotramatic amblyopia, and amaurosis, exhausting diseases, and severe fevers; it sometimes occurs with intra-ocular hemorrhage; it may be part of the epileptic aura; it is said to be caused by coffee in rare instances. Blue vision is occasionally complained of by patients suffering from retinitis albuminurica and detachment of the retina, and may also follow the use of cannabis indica. *Green vision* (*chloropsia*) is a rare symptom of detachment of the retina, optic-nerve atrophy, and aphakia as the result of cataract extraction. Blind eyes occasionally are conscious of colored lights, probably due to irritation of the visual centres.

It seems probable that chromatopsia may be due either to central irritation or to local causes. No entirely satisfactory explanation of the phenomenon has yet been offered. Fuchs attributes red vision to the action of strong light on the visual purple and its slow regeneration under less intense light; but the absence of visual purple at the macula upsets this theory. Snellen believes it to be due to the coloring of white light by its passage through the translucent and vascular lids and choroid, and the subsequent diffusion of this reddish light over the retina. After the extraction of cataract, upon exposure to bright light, the lids are partly closed; there is thus a small central pupillary opening for white light, while the periphery of the retina is flooded with red light which has come through the lids. When the intensity of the illumination is reduced, the red perception of the periphery changes to a complementary green as a result of fatigue, while central vision appears red by contrast. The blue vision after cataract extraction is attributed by Burnett to fatigue of the retina as a result of long-continued exposure to light rendered yellow by passage through amber-colored cataracts, giving blue as a residual sensation in white light.

Toxic Chromatopsia.—Colored vision, usually yellow (*xanthopsia*), is one of the symptoms of the poisonous effects of certain drugs, of which santonin is the most common example; this agent may, however, produce green vision, or rarely red or blue vision. Other drugs which may produce chromatopsia are amyl nitrite, picric acid, chromic acid (as a result of local applications), osmic acid, digitalis, carbonic oxide, and tobacco. Xanthopsia also occurs as an early symptom of catarrhal jaundice, being due probably to the discoloration of the dioptric media by bile pigments; it is seen after dazzling from electric light, and may accompany nyctalopia.

Charles H. May.

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